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"I would have everie man write what he knowes and no more."—MONTAIGNE

BRITISH JOURNAL OF ANAESTHESIA

SYMPOSIUM ON CURRENT TRENDS IN OBSTETRIC ANALGESIA
(September 3, 1978, Paris)

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INTRODUCTION

In Paris, on Sunday, September 3, 1978, just before the 5th European Congress of Anaesthesiology, a symposium took place on Current Trends in Obstetric Analgesia. The symposium received generous financial and other support from AB Astra, Sweden, and we are grateful to many members of their staff who contributed to the organization of the meeting. The proceedings of the symposium, including the discussions, are reported in this additional issue of *British Journal of Anaesthesia.*

D. B. Scott

OPENING REMARKS

PROF. J. LASSNER (PARIS): On behalf of the Organizing Committee of the European Congress I would like to welcome you to this symposium, which is being held in parallel with the main congress. In approaching the problem of pain relief in obstetrics we must always remember that for most women pregnancy is not an illness. By treating them like sick people we can arouse strong protests in many countries. We must be careful not to arouse hostility, particularly in the general public, by over-powering normal people with our modern technology. I believe that the first and most important voice to be heard in regard to analgesia in labour should be that of the mother. Methods should be made available and offered to the mother; they should not be pressed on her against her will. This symposium will outline the many and varied methods of analgesia during childbirth.

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PERIPHERAL MECHANISMS AND PATHWAYS OF PARTURITION PAIN

J. J. BONICA

Although the gross anatomy of the nerve supply to the uterus was described by Galen and others (cited by Keele, 1957) and the connections of these nerves to the spinal cord were defined in the early nineteenth century, it was not until 1893 that Head, following careful study of the areas of skin hyperalgesia in parturients and in women with disease of the cervix, concluded that the pain from the body of the uterus was transmitted by the 10th to 12th thoracic and occasionally the 1st lumbar nerves while that from the lower uterine segment and cervix was transmitted via S2–4, and sometimes S1 spinal segments. For 40 years Head's views were disputed by anatomists and neurophysiologists. Clinical observations during caudal anaesthesia prompted Cleland (1933) to begin a long series of elegant animal studies using the well-established MacKenzie (1912) method of visceromotor reflexes to determine the afferent supply from the uterus. He used the evidence of the analogy of the afferent nerve supply in dog and man (Johnson, 1906) and concluded that pain from the uterus in humans entered the spinal cord at T11 and T12. In 1932 he successfully applied his concept to parturients by using paravertebral block, also a well-established technique which had been widely used to define pain pathways from other viscera (Mandl, 1926). He noted that paravertebral block with 1% procaine 5 ml at T11 and T12 nerves bilaterally produced consistent relief of pain during the first stage of labour. He concluded that the pain of labour has two components: "(a) that due to uterine contractions which is transmitted by afferent fibres through the 11th or 12th thoracic root; (b) that due to stretching of the birth canal which is transmitted through certain undetermined sacral roots".

Although Cleland did not mention the nerve supply to the cervix, his conclusions were interpreted to mean that the cervix is supplied by the sacral segments. Consequently, many textbooks, and an authoritative paper on the pain of labour (Javert and Hardy, 1950) stated that the pathways of labour pain involved two separate sets of afferent fibres: those which transmit pain from the body of the uterus to the spinal cord at T11 and T12, and those that transmit pain from the cervix and birth canal, contained in the pelvic nerves (nervi erigentes) and entering the spinal cord at S2–4. It had been long established that pain from the perineum was transmitted via afferent fibres in the pudendal nerves which also enter the spinal cord in the middle three sacral segments (King, 1916). On the basis of these views of the nerve supply to the uterus, it was advocated that pain of labour could and should be relieved with blockade of the two thoracic segments during the first stage, and of the sacral segments during the second stage.

My own observations and those of others were at variance with the claim that the cervix is supplied by the sacral segments. Moir (1939) and Theobald (1946) had found dilatation of the cervix to be an important source of pain in the first stage. This pain could be relieved completely by paravertebral block of lower thoracic nerves or lumbar sympathetic block. Following surgical section of the superior hypogastric plexus (so-called presacral neurectomy), used for dysmenorrhea, labour was painless (Rysanek and Cavanagh, 1958). (Since none of these procedures involves the nervi erigentes, it was difficult to accept that the cervix was supplied by the sacral afferents.) Another discrepancy was that true saddle block involving only the sacral segments did not affect the pain of the first stage of labour. Subsequently, I doubted that the spinal segments between L1 and S2 are not involved in pain of parturition, for many of my patients complained of pain and discomfort in the lower thighs and legs.

Over 20 years I studied 210 patients (185 parturients and 25 patients undergoing gynaecological surgery) (Bonica, 1979). The technique used to define the various nociceptive pathways included paravertebral somatic nerve block, lumbar sympathetic block, segmental extradural block with one, two and three catheters and trans-sacral block. By injecting small

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volumes of local analgesic it was possible to block discretely one, two, or more segments. The influence of block of different spinal cord segments was studied in patients undergoing surgery in whom pain was evoked by rapid stretching of the cervix, either manually or with a balloon, before and after block of various segments, and in parturients in whom the pain produced by manual stretching of the cervix and the pain produced by uterine contractions, the perineal pain of the second stage and other pain associated with labour were evaluated before and after block.

In parturients it was found that manual dilatation of the cervix increased the pain associated with the other contractions. Moreover, it was found that paravertebral block of T11–12 produced complete relief of contraction pain during the early part of the first stage but only partial relief of pain associated with the intense contraction of the late first and second stages. Blockade of T10 and L1 relieved these pains completely. Similar results were obtained by limited segmental extradural block involving two, three or four segments. Lumbar sympathetic block relieved experimental pain and pain of uterine contractions but not any of the other pains. Trans-sacral block with single segments of S2–4 produced little or no relief of perineal pain, but blockade of two segments produced partial relief, and of three, complete relief.

Although reports of these findings were published (Bonica, 1960, 1967, 1974), the concept that the cervix is innervated by sacral segments prevails in anatomy and obstetric books. Moreover, many anaesthetists ignore the involvement of the lower lumbar and upper sacral segments in the pain of parturition.

PAIN OF THE FIRST STAGE OF LABOUR

Mechanisms

Although the exact mechanisms have not been determined, there are data which suggest that, during the first stage of labour, pain results from dilatation of the cervix and contraction and distension of the body of the uterus.

The role of *dilatation of the cervix* and the distension, stretching or tearing of tissues is supported by: (1) the observation that stretching of smooth muscle is an adequate stimulus for visceral pain (Bonica, 1953); (2) the correlation between the degree of dilatation of the cervix and intensity of pain; (3) the correlation between the onset of uterine contraction and the onset of pain. There is a lag of 15–30 s before pain is experienced (Caldeyro-Barcia and Poseiro, 1960), longest in the early stages of labour and lessening as labour progresses. This may be the time to develop amniotic fluid pressure of 15 mm Hg greater than tonus—the minimum pressure for distending the lower uterine segment and cervix (Caldeyro-Barcia and Poseiro, 1960); (4) during Caesarean section with abdominal field block, the exposed but unanaesthetized uterus can be incised and palpated without sensation to the conscious patient, while palpation and stretching of the cervix produce discomfort similar in quality and location to that experienced during labour (Moir, 1939; Javert and Hardy, 1950; Bonica, 1960); (5) sudden and wide dilatation of the cervix in parturients causes pain similar in quality, distribution and intensity to that produced by uterine contractions. Dilatation of the cervix in non-pregnant patients produces pain which is referred to the lower thoracic dermatomes (Moir, 1939; Theobold, 1946; Javert and Hardy, 1950; Paul et al., 1956; Bonica, 1960).

Progressively more intense contractions of the uterus contribute significantly to the pain of the first and second stage of labour. Earlier writers suggested that pain resulted from pressure on nerve endings between the muscle fibres (Reynolds, 1949) contraction of the ischaemic myometrium (Moir, 1939) and inflammatory change in the uterine muscles (Woodbury, 1947; Reynolds, 1949). Recent data cast doubt on the last two mechanisms. It has been shown that, during intense sustained uterine contractions, the myometrium receives greater perfusion than between contractions (Novy, 1972). Moreover, there is no evidence of an inflammatory process in the uterine muscles. It is most likely that the pressure and stretch of the uterine muscles stimulate high threshold mechanical and polymodal nociceptors. Distension of the smooth muscles of the hollow viscus or intense contractions against obstruction of its outlet, or both, cause visceral pain. Moreover, sudden distension of the uterine cavity produces reflex responses characteristic of pain (Cleland, 1933). These are particularly important mechanisms of the severe pain experienced by women with dystocia or persistent posterior position, even when cervical dilatation is minimal. Intense obstruction and distension of the lower uterine segment probably provide the nociceptive stimulus. The recent evidence that repeated stimulation of high threshold nociceptors reduced their threshold may explain in part the progressive increase in the intensity of labour pain. It is also possible that the contractions cause cellular breakdown with the liberation of "pain producing substances" which diffuse into the extracellular space and decrease the threshold of visceral nociceptive afferents.

The claim that contraction of the cervix following fear-induced hyperactivity of the sympathetic nervous system produced tension which in turn caused pain (the so-called vicious circle of fear–tension–pain) (Dick-Read, 1933) is unwarranted. The cervix is composed mostly of connective tissue with very little muscle and elastic tissue (Danforth, 1954). Sensitive tochography has shown that during uncomplicated childbirth the lower uterine segment and cervix manifest only a small contractile force during the early phases of labour, becoming even weaker at the end of the first stage (Caldeyro-Barcia and Poseiro, 1960); thus when the pains of labour are most severe, the cervix contracts least.

Peripheral pathways

Noxious impulses from the cervix and uterine body are transmitted to the spinal cord by A delta and C afferents carried in the sympathetic pathways and passing through (a) the uterine and cervical plexuses, (b) the pelvic, inferior hypogastric, middle hypogastric and superior hypogastric plexuses, (c) the lumbar and lower thoracic sympathetic chain, (d) the white rami communicantes associated with the T10, T11, T12 and L1 nerves, (e) the posterior roots of these nerves to the spinal cord (fig. 1).

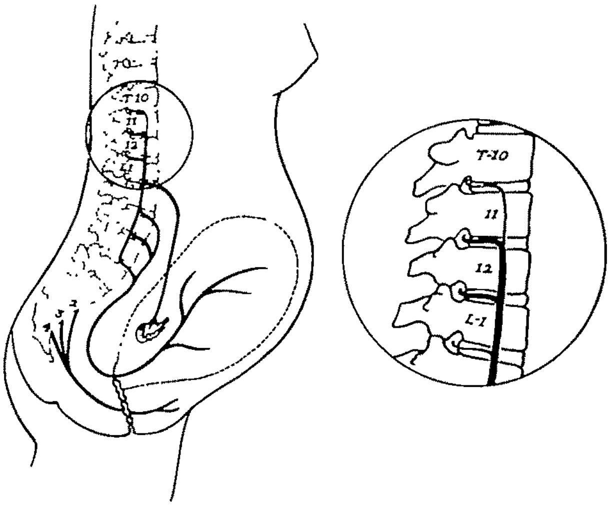

FIG. 1. Schematic diagram of the principal nociceptive pathways for pain of parturition. Nociceptive impulses from the uterus pass to the spinal cord via afferent fibres associated with the sympathetic nerves and into the spinal cord via the nerve roots of T11 and T12 during the early part of the first stage, but as the contractions become more intense the two adjacent segments (T10, L1) become involved. Pain from the perineum is transmitted to the pudendal nerve. Not shown in the diagram are the pathways for "other" pain caused by pressure and stretching of pelvic structures discussed in the text.

The cervix is supplied by the same spinal cord segments (T10–L1) as is the body of the uterus. Theobald (1946) noted that stimulation of the cervix with a faradic current or by manual dilatation caused pain which was referred to the same dermatomes (in the lower abdomen) as was faradic stimulation of the body of the uterus. Paul and others (1956) distended a balloon in the cervical canal causing sharp, cramp-like pain in the mid to lower abdomen. Finally, if we assume that cervical dilatation contributes to the pain of uterine contraction, the fact that such pain can be eliminated with segmental or paravertebral block limited to T10–L1 adds further evidence that the cervix is supplied by the same segments as the uterus.

I believe that Head, and other workers, developed the misconception that the cervix and lower uterine segments are supplied by nociceptive fibres in the sacral segments because the pain of uterine contraction is frequently referred to the skin and soft tissue over the lower lumbar spine and sacrum. However, the cutaneous branches of the posterior divisions of the lower thoracic, lumbar and sacral nerves migrate caudally for a considerable distance before they innervate the skin and subcutaneous tissue overlying the spinal column, and the adjacent paravertebral region for about 8–10 cm (Pernkopf, 1943; Bonica, 1960, 1967). Thus, the cutaneous branches of the posterior division of T10 supply the skin at the level of the spinous processes of L2 and 3 vertebrae; those of T11 supply the skin overlying L3 and L4, while T12 supplies the skin over L5 and S1, and L1 the tissues over the middle portion of the sacrum. The posterior division of L4 does not give cutaneous branches and those of L5 to S3 inclusive supply the tissues over the lower third of the sacrum and the posterior part of the buttock, while those of S4 and S5 and the coccygeal nerves supply a very small area of tissue overlying the coccyx. Unless these anatomic facts are appreciated, the reference of pain to these areas of the "low back" may be interpreted as involving the nerves which exit from the underlying vertebrae and the sacrum (L3–S5 spinal segments).

PAIN OF THE SECOND STAGE OF LABOUR

Once the cervix is dilated there is little or no further stimulation from its structures, but the contractions and distension of the uterus continue to cause pain in the areas of reference which the pain is usually less intense than in the first stage. The impact of the presenting part on pain-sensitive structures in the pelvis and distension of the outlet and perineum become new sources of pain. Like other pain caused by stimulation of superficial somatic structures, the perineal pain is sharp and well localized and is largely a result of distension, stretching and tearing of fascia, skin and subcutaneous tissues and pressure on the skeletal muscles of the perineum (King, 1916). Pudendal nerve block eliminates this pain completely (Klink, 1953; Bonica, 1967).

In the late part of the first stage and during the second stage, there is stimulation of pain-sensitive structures in the pelvic cavity which usually produces only mild referred pain. The structures involved and the area of pain references are: (1) traction and pressure on the adnexa: pain referred to T10–L1; (2) stretch of the pelvic parietal peritoneum and the structures it envelopes including the uterine ligaments: pain referred to the sacral segments; (3) pressure on and stretch of the bladder, urethra and rectum: pain referred to the sacral segments; (4) stretch of, and pressure on, ligaments, fascia and muscles of the pelvic cavity with pain reference to the lower lumbar and sacral segments; and (5) pressure on one or more roots of the lumbosacral plexus: pain referred to the back of the thigh and perhaps to the legs. In patients with a persistent posterior position of the presenting part or with dystocia, there is intense stimulation from uterine distension and the pelvic structures that produces severe pain in the low back and thighs. To relieve such pain segments L2–S5 must be blocked.

CENTRAL NOCICEPTIVE (PAIN) MECHANSIMS

It is well known that the dorsal horn contains many varieties of neurons and synaptic arrangements (Rexed, 1952; Scheibel and Scheibel, 1968; Bonica and Albe-Fessard, 1976) which permit reception and transmission and a high degree of sensory processing, including local abstraction, integration, selection and division (Wall, 1967; Bonica, 1977).

Recent evidence also makes it clear that nociceptive afferents terminate in laminae I–VI, but especially in I, IV, V and VI of the dorsal horn where they synapse directly with second-order neurons. There are three distinct types of second-order nociceptive neurons in the dorsal horn (Mayer and Price, 1979). Some neurons found mainly in the marginal layer of lamina I receive input exclusively from A delta high-threshold mechanoreceptive afferents. Other nociceptive neurons, also found primarily in the marginal layer, receive excitatory synpatic effects of high-threshold A delta mechanoreceptive afferents, from A delta heat-nociceptive afferents and from C polymodal nociceptive afferents. These marginal cells have connections with cells in the substantia gelatinosa of the same and neighbouring segments and project their axons to the contralateral cord and ascend cephalad in the spinothalamic tract. The third type of neurons, which exist within the laminae I–VI, but are concentrated in laminae IV, V and VI, are wide, dynamic-range neurons which receive synaptic excitatory effects from large myelinated (A beta) low-threshold mechanoreceptive afferents, A delta high-threshold mechanoreceptive afferents and C polymodal nociceptive afferents. As a result of this extensive convergence these cells respond with increasingly higher frequency of impulse discharge to touch, pressure and noxious pinching. Some of these neurons send axons to the ventrolateral white matter of the spinal cord, both ipsilaterally and contralaterally, to make up the spinothalamic tract. Particularly important in obstetric anaesthesia is the fact that all of the lamina V cells which respond to visceral high-threshold afferents also respond to low-threshold cutaneous afferents from an area of skin supplied by the same spinal cord segments (Wall, 1967). Thus, these lamina V cells provide the neural basis for the phenomenon of referred pain which occurs during each uterine contraction (fig. 2).

CLINICAL IMPLICATIONS

The new and old data about the mechanisms of pain in parturition have important implications for the obstetric anaesthetist. Relief of such pain, especially when it is severe, has important benefits because it eliminates segmental and suprasegmental reflex responses that may prove deleterious to the mother and infant. Intense noxious stimulation produces inhibition of gastrointestinal function, causing retention of food and fluid, urinary retention and inhibition of uterine activity that may impair contractions (Maltau and Andersen, 1975). These responses are aggravated by a general increase in sympathetic tone which increases further inhibition of visceral function and increases the cardiac output, producing increased arterial pressure and hyperventilation. The cerebral cortical responses, particularly anxiety and apprehension, also contribute to ventilatory changes and to the hypothalamic hyperactivity.

During labour, pain-induced hyperventilation may be so severe as to produce marked respiratory alkalosis with consequent marked decrease in cerebral blood flow and uterine blood flow (Bonica, 1972). Studies in pregnant ewes have shown that pain-induced

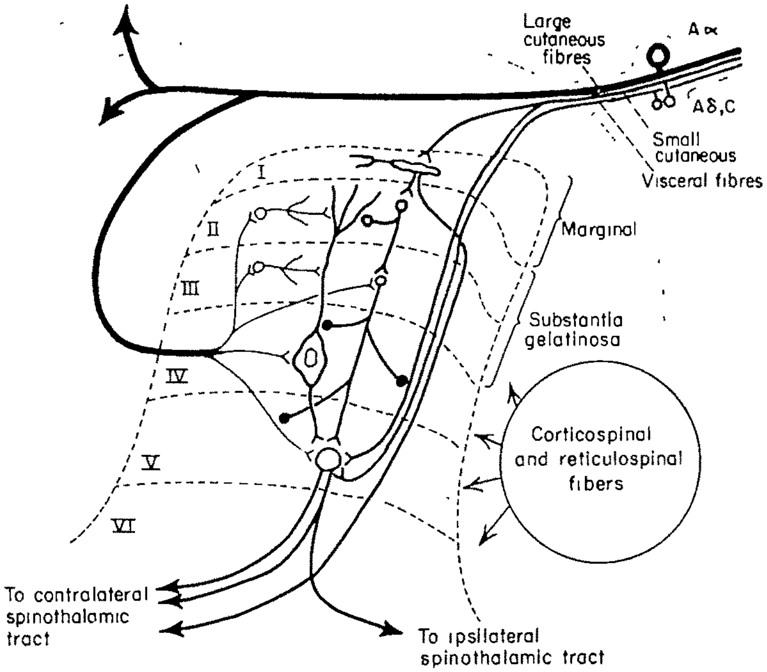
Large cutaneous fibres
A α
A δ, C
Small cutaneous
Visceral fibres
I
II
III
IV
V
VI
Marginal
Substantia gelatinosa
Corticospinal and reticulospinal fibers
To contralateral spinothalamic tract
To ipsilateral spinothalamic tract

FIG. 2. Simple schema of dorsal horn of spinal cord. Note large fibres break up into long ascending and short descending to make up dorsal columns and give off collateral branches that enter dorsal horn and make contact with numerous interneurons. Small cutaneous fibres synapse on lamina V cells. Convergence of cutaneous and visceral fibres on latter cells may be basis for referred pain. Laminae I and V cells, and possibly IV and VI, send axons primarily to contralateral cord and ascend as spinothalamic tract. Supraspinal descending tracts also make connection with dorsal, ventral and ventrolateral horn cells, and thus may modulate their output.

liberation of catecholamines (primarily noradrenaline) further decreases uterine blood flow and uterine contractility. With inadequate relief of labour pain, maternal oxygen consumption is increased (Sangoul, Fox and Houle, 1975) and there is an increase in maternal and fetal metabolic acidosis (Pearson and Davies, 1973a, b, 1974a, b; Thalme, Belfrage and Raabe, 1974). The combination of decreased uterine blood flow and metabolic acidosis are likely to endanger the fetus. In addition, severe labour pain may produce significant postpartum emotional reactions (Bonica, 1967).

There is neurophysiological and psychological evidence that providing patients with information, developing confidence, motivation and encouragement during the preanaesthetic visit are likely to reduce anxiety and the physiological response to it that occurs in many patients before an anaesthetic (Chapman, 1978). In addition to improving the emotional well-being of the patient, this is likely to reduce the need for preanaesthetic and anaesthetic drugs during the labour and delivery, and anxiety and pain during the postpartum period.

Finally, it is important to stress the clinical implications of recent findings about peripheral nociceptive pathways involved in parturition pain. It is well established that A delta and C nociceptive afferents can be completely blocked with small concentrations of local anaesthetics. Moreover, during the first stage of labour a segmental extradural block limited to T11 and T12 during the early part and later expanded to involve the two adjacent segments is sufficient to provide virtually complete pain relief. Limiting the block to these segments has two major advantages: (1) it entails the use of small volumes (3–4 ml) of small concentrations of local anaesthetics and thus decreases maternal and fetal drug toxicity; and (2) avoiding block of the sacral segments early in labour obviates interfering with Ferguson's reflex and the cardinal mechanism of internal rotation of the fetal presenting part (Bonica, 1967). During the latter part of the first stage and early second stage, noxious stimulation of pelvic structures will produce pain involving the lower lumbar and upper sacral segments and will require extension of analgesia caudad. However, since this still does not include the middle three sacral segments, it will not interfere with the aforementioned two mechanisms.

When perineal pain becomes moderate to severe during the second stage, analgesia (without muscle paralysis) of the sacral segments may be achieved by the continued use of small concentrations of local anaesthetics. Although the perineal analgesia eliminates the afferent limb of the reflex urge to bear down, the parturient still retains good motor function of the abdominal muscles and the diaphragm, so that these can be voluntarily contracted to produce sufficient additional intra-abdominal pressure to help the uterus expel the infant spontaneously if such a delivery is desirable. After internal rotation takes place, an injection of a greater concentration of the local anaesthetic can be given to produce perineal relaxation, which now is appropriate and beneficial because it facilitates vaginal delivery, especially if outlet forceps are used.

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DISCUSSION

Dr A. Doughty (Kingston-upon-Thames): I would be interested to hear an explanation of some atypical pain patterns which sometimes occur in labour as, for instance, abdominal pain which may remain unrelieved by an extradural block but disappears when the bladder is emptied. Very occasionally one sees unilateral pain, by which I do not mean partial relief from an inadequate extradural, but pain before the extradural is given which is limited to one side only. Sometimes contraction pain may be referred down the posterior aspect of the thigh and this requires block of S2, 3 and 4 segments: a few women also complain of perineal pain during the first stage of labour with a high fetal head and again it is necessary to block the sacral segments even in the first stage of labour.

Dr J. Bonica (Seattle): I think all these types of pain can be explained in terms of our present knowledge of the mechanisms of pain. In my view, when the pain is most severe in the back, it is due to the posterior part of the cervix being dilated more rapidly than the anterior part.

Dr M. Rosen (Cardiff): When talking about particular spinal segments being involved in the pain of uterine contractions, how can you be certain exactly which ones are involved, given that extradural blocks are often very difficult to confine to particular nerves, and given the overlap in the nerve distribution?

Dr Bonica: The most convincing evidence comes from the use of paravertebral spinal nerve block in which the nerves are individually located and blocked with small volumes of local anaesthetic.

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SYSTEMIC AND INHALATION ANALGESIA

M. ROSEN

Pain relief is not life saving for the mother or her baby, other than in exceptional circumstances. Therefore, comparisons of methods of pain relief should include consideration of safety, effectiveness and cost. In any case, dependence on a single technique for the management of labour pain is unsound, since it assumes falsely that there is uniformity of maternal requirements.

Although safety is never absolute as far as the mother is concerned, inhalation analgesia and narcotics are very safe. There has been no death associated with these techniques and drugs in more than 15 million deliveries (Department of Health and Social Security 1975). No other method approaches this record. That is the main reason why pethidine and "gas" are so widely used in the United Kingdom under the supervision of midwives, although under strictly controlled conditions.

Narcotics and tranquillizers

I.m. pethidine is prescribed for about 70% of mothers in labour (Chamberlain et al., 1975). Usually the timing of administration is left to the midwife's judgement, enabling a prompt response to the mother's requests. The wide difference in the chosen dose (50–150 mg) arises mainly from concern over the depressant effects of pethidine on the newborn. However, in some women pethidine is associated with poor pain relief, resulting in drowsiness and an unpleasant, almost dissociated, state (O'Driscoll and Stronge, 1973). It is possible that smaller doses may be made more effective when reinforced by relaxation techniques, and when loneliness, fear and anxiety are minimized (O'Driscoll and Stronge, 1973). Unfortunately, optimum conditions exist in only a few obstetric units, most of which are imperfectly organized. Also, comparisons are lacking between the dose required under optimum and suboptimum conditions, so that the routine dose is usually dependent upon personal prejudice. Studies indicate that pethidine 50–100 mg i.m. provides pain relief for only about 40% of patients (Moore, Carson and Hunter, 1970; Holdcroft and Morgan, 1974) whereas 50–60% of patients claim satisfactory pain relief with an i.m. dose of 150 mg (Grant, Holt and Noble, 1970). Biological variation gives rise to differences in drug requirements which cannot be met by any standard i.m. dose. Individual need can be met more satisfactorily by administering pethidine i.v. according to patient demand. This can be achieved safely, and without increasing medical participation, utilizing an apparatus programmed by the clinician (Evans et al., 1976; McCarthy et al., 1976). The total dose of analgesic prescribed by the clinician is delivered i.v. by a syringe pump which is set to deliver any increment between 1 μg and 999 mg. The speed of injection can be controlled to reduce side-effects from a peak blood concentration; 3–4 min has been used in labour. The minimum duration between two increments can be set at any interval from 0 to 99 min. This interval is necessary to avoid overdose by allowing the mother to appreciate the effects of the increment before a further demand. In labour an interval of 10 min has been used, which ensures that two or three contractions elapse for assessment. Initially an incremental dose of 0.25 mg kg^{-1} was chosen empirically, but it has since been shown by us that it is not necessary to use such a precise dose, provided that the increments are not so small that, even cumulatively, they have little effect, or are so large that undesirable side-effects result from each. It has been found that on offering an incremental dose of 0.125, 0.25, or 0.375 mg kg^{-1} to randomly selected mothers in labour, the times between demands were significantly longer with the higher incremental doses (Hogg, 1977). This is presumably a result of "feedback" because the mother is balancing the maximum pain relief achievable with pethidine (rarely perfect) against undesired side-effects, such as drowsiness. This phenomenon is present also when inhalation analgesia is used (Latto, Molloy and Rosen, 1971).

The apparatus has been tested in an obstetric unit in which extradural analgesia was not available. Mothers who were willing to have pethidine had either

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100 mg i.m. (the routine dose in that unit) or i.v. by self-administration usually with 350 mg available. The total dose of pethidine was prescribed by the doctor, who inserted the i.v. cannula. The apparatus was prepared and supervised entirely by midwives according to prepared instructions. An incremental dose of pethidine 20 mg was administered to all mothers of 60–80 kg weight, and 15 mg for lighter or 25 mg for heavier mothers. In 103 primagravidae, the mean dose of pethidine demanded i.v. was 217 mg (range 60–600 mg) compared with 171 mg (range 100–300 mg) administered by the i.m. route. Seventy-three per cent of the mothers who had self-administered pethidine reported complete or considerable pain relief, compared with 40% of those who had pethidine i.m. ($P < 0.005$). The apparatus was used for approximately 25% of deliveries and about three apparatus were required to cover simultaneous demands in the unit (2500 deliveries per annum). The apparatus was found to be most valuable in early labour, since there was more time to balance the need for analgesia. Other analgesics are being tested since pethidine is not ideal in some respects.

Pethidine causes nausea and vomiting in about 15% of patients and some clinicians administer metoclopramide 10 mg or perphenazine 5 mg which reduces the frequency to 5% or less (McGarry, 1971). However, it is more logical to treat those who suffer nausea or vomiting than to administer anti-emetics routinely to every mother.

Effects on the baby

Pethidine administered to the mother during labour depresses the respiration of the newborn at birth (Rosen et al., 1969) and for at least 48 h afterwards (Wiener, Hogg and Rosen, 1977a, b). It has been suggested, from information derived in a retrospective study of Apgar scores, that pethidine administered more than 4 h or less than 1 h before delivery has less effect on respiration at birth (Shnider and Moya, 1964). However, urinary excretion of pethidine is greater and significantly so, up to a dose-to-delivery interval of 5 h (Hogg et al., 1977). Although pethidine depresses respiratory adaptation at birth, reducing the Apgar score by 1–2 points (Rosen et al., 1969), this is rarely substantial as a sole factor. However, the effects of pethidine may be more serious for the premature infant (Maternal and Child Health Service, 1967), although no definite evidence exists to determine if this is so.

After birth the effects of pethidine administered to the mother can be detected in the neonate. Pa_{CO_2} is increased for at least 24 h (Koch and Wendel, 1968), there is a depression of feeding measures for days compared with children of mothers who received no drugs in labour (Kron, Stein and Goddard, 1966; Dubignon et al., 1969), and there is depression of other neurological functions (Richards and Bernal, 1972; Brackbill, Kane and Manniello, 1974; Weiner, Hogg and Rosen, 1977a, b). However, naloxone 40 μg i.v. when compared with placebo, administered at birth (Evans et al., 1976), resulted in a significant decrease in Pa_{CO_2} and an increase in alveolar ventilation for about 30 min after birth (Evans et al., 1976). After 4 h no difference could be found between the groups (Wiener, Hogg and Rosen, 1977a, b). When naloxone 200 μg or placebo was administered i.m. at birth, significant differences were present up to 48 h in ventilatory, feeding and neurobehavioural responses. Indeed the naloxone-treated babies seemed similar to babies whose mothers did not receive drugs during labour. It seems likely that naloxone can reverse the effects of pethidine in the newborn. It may now be more rational to relate pethidine dose to maternal requirements, with less concern about the fetus.

Diazepam

Diazepam reduced the total dose of pethidine required in one trial which was not double-blind (Friedman, Niswander and Sachtlebern, 1969). Since it is difficult to conceal the effects of diazepam, this effect may have been artefactual. Diazepam 0.3 mg kg^{-1} i.m. improved the maternal opinion of pain relief, but the required dose of pethidine was unchanged (Davies and Rosen, 1977). During labour diazepam is now mainly reserved for the management of severe pre-eclampsia or eclampsia.

Diazepam can cause severe hypotonia in the newborn at birth and subsequent hypothermia and these effects may be evident for several days. It is recommended therefore that no more than 30 mg of diazepam be administered to the mother during labour (Cree, Meyer and Hailey, 1973).

Inhalation analgesia

In the United Kingdom inhalation agents are self-administered intermittently by the mother in labour, under the supervision and encouragement of a midwife. A fixed concentration of 50% nitrous oxide in oxygen (Entonox) or 0.35% methoxyflurane in air are used commonly, although trichloroethylene 0.5% is still available. The effectiveness of self-administered inhalation depends upon how closely peak brain concentration can be made to coincide with the peak of the contraction, that is with the greatest pain. In the periods between contractions the mothers' blood concentration is reduced and she is therefore less likely to fall asleep or become semi-conscious. In that way maximum suppression of painful stimuli can be attained with reasonable safety. It is most important as an element of safe practice that the mask should only be held on the mother's face by herself; then if she falls asleep the mask can fall away and she will breathe air.

When inhalation analgesia is used effectively about 70% of mothers report considerable or complete pain relief (Rosen et al., 1969; Holdcroft and Morgan, 1974), but accurate timing of inhalation is essential to successful administration. With a soluble agent such as methoxyflurane this is achieved more easily since the mother regulates her breathing to attain optimum blood concentration (Latto, Molloy and Rosen, 1971), and in any case the fluctuations in blood concentrations of methoxyflurane during and between contractions are about half the peak concentration. Under optimal conditions about 90% of mothers having methoxyflurane consider pain relief as complete or considerable (Major, Rosen and Mushin, 1967; Rosen, 1975). However, it is a drawback that about one-third of mothers and midwives dislike the smell of methoxyflurane. Therefore Entonox, which has no smell, is the more popular agent. The relative insolubility of nitrous oxide renders it much more difficult for the mother and midwife to judge the timing of inhalation and the rapid uptake and excretion are reflected in less satisfactory results.

A method has been evolved which attempts to reduce fluctuation in blood concentrations by ensuring a steady blood concentration between contractions so that the time needed to reach peak concentration can be reduced during intermittent administration. A flow (5 litre min^{-1}) of Entonox is inhaled continuously through a nasal catheter while Entonox is breathed through a mouthpiece during uterine contractions (Dolan and Rosen, 1976). It was found in controlled trials that more than 70% of mothers were willing to accept the method during labour. The mean concentration of end-tidal nitrous oxide between contractions was 14.8% with nitrous oxide administered nasally compared with only 2% with intermittent nitrous oxide only. There is a substantial improvement in the mothers' opinions of the pain relief, and the method is undergoing wider field trials (Arthurs and Rosen, 1979).

Effects on the baby

Inhalation agents have little effect on fetal-neonatal respiratory adaptation and are excreted rapidly when respiration is established. After continuous inhalation, end-tidal nitrous oxide decreased to less than 2% 8 min after birth (Arthurs and Rosen, 1979). Methoxyflurane is metabolized by the neonate and low concentrations of fluoride can be found in neonatal urine up to 48 h after birth (Weiss and deCarlini, 1975). However, there has been no evidence of renal abnormality.

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DISCUSSION

DR M. FINSTER (NEW YORK): I was very interested in your remarks regarding the variability in the dosage of pethidine between patients. However, your slide did not show the important factor of time. It is not the total dose of pethidine given during labour that is so important, rather the dose per hour. Do you have any data on this? In addition, am I right in saying that although your babies in the naloxone study received only one dose of naloxone their arterial carbon dioxide tensions were lower than in the control group for as long as 48 h?

DR ROSEN: Of course time is very important and, when this is allowed for, the variability between patients is narrowed. However, it is still very considerable, some patients requiring as much as six times more than others.

We were also very surprised to find that a single i.m. dose of naloxone had such a long-lasting effect. Because of this we repeated the study and found exactly the same results. From measurements of drug concentrations we are now of the opinion that naloxone is pharmacologically active for at least 12 h. However, it may well be that naloxone triggers other mechanisms which are responsible for the much longer-lasting respiratory effects. For instance naloxone-treated babies all fed better than the control group, thus giving the baby an increased acid fluid load. This and other factors, therefore, may well lead to a much more rapid excretion of pethidine in the treated neonate.

DR BONICA: I think that the use of maternal mortality rates in assessing obstetric analgesia is far too crude. There should be no mortality in properly conducted analgesia by whatever method. It is much more important to look at morbidity in both mother and neonate and when this is done for abnormal deliveries you will see a clear advantage to local anaesthetic methods.

DR ROSEN: Yes, I quite agree with that and there is some evidence that extradural block may be important for the delivery of premature infants (Maternal and Child Health Service, 1967). However, I did just want to point out that all hospitals do not have the same high standards and it is towards improving standards that we must direct most of our effort.

DR H. H. BRÄUTIGAM (HAMBURG): I cannot agree that the use of pethidine is free from dangers to the fetus and neonate. If the fetal heart rate is carefully monitored, you will see that the administration of pethidine often has a deleterious effect on the fetus. Neonatal morbidity and mortality are much higher when narcotic analgesics are given.

DR ROSEN: We carry out careful monitoring of the fetal heart rate during labour and do not see abnormalities in the heart rate patterns following the administration of pethidine.

I know of no evidence, statistical or otherwise, to show that pethidine administered properly has any long term deleterious effect on the baby. It is, of course, extremely important to avoid aorto-caval compression during labour, this is so regardless of the type of analgesia given.

Dr Doughty: I am surprised that only 60% of your patients receiving extradural block were completely satisfied with their analgesia.

Dr Rosen: The figures I quoted for extradurals are, of course, those which are obtained by the trainee registrar anaesthetist. Nevertheless, many extradurals have to be given by trainee anaesthetists and the results are bound to be less good than those given by very experienced people.

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REGIONAL TECHNIQUES OF ANALGESIA IN LABOUR

A. HOLLMÉN

Regional analgesia techniques may offer the most effective method of pain relief in labour. However, they may contribute to morbidity and mortality. Therefore there is a need for skill and experience to prevent complications, for apparatus for treatment of complications and for continuous monitoring. This review is of the present practice and its background.

A recent questionnaire in the U.S.A. (Hicks, Levinson and Shnider, 1976) showed that at major university training centres approximately 70% of patients received regional analgesia for pain relief (lumbar extradural block 24%, caudal block 6%, pudendal block 26% and low spinal block 21%). Dr J. S. Crawford (personal communication) found that the frequency of extradural analgesia in major hospitals in Birmingham was 2–3% of all obstetric anaesthesia. He forecasts that the frequency of extradural analgesia in England may increase during the next 10 years to about 30–50%. Parenteral analgesics or inhalation analgesia are used for pain relief in the majority of deliveries in the Nordic countries. Pudendal block, administered to approximately 49% of patients, was the commonest of the regional techniques employed in Sweden for relief of labour pains. About 4% received paracervical analgesia, but extradural analgesia was given to only 1.7%. The frequent use of pudendal block in Sweden is explained by the fact that it may be performed by midwives. In Finland lumbar extradural analgesia was given to 2% of obstetric patients at university hospitals in 1977. However, in both Finland and Sweden the use of lumbar extradural block is increasing. Severe pain in labour is experienced by 15–20% of Finnish mothers (Hollmén et al., 1970; Lappi, Kivalo and Teramo, 1978).

Paracervical block (PCB)

At the time of the introduction of PCB for the relief of pain of cervical dilatation in both the U.S.A. and Europe, in the 1960s, the fetal bradycardia often associated with it was not regarded as clinically significant. Teramo and Widholm (1967), Asling and others (1970) and Shnider and others (1970) showed that fetal bradycardia in connection with PCB is often accompanied by fetal acidosis and depression of the newborn. These factors and reports of intrauterine fetal death associated with PCB led to a decrease in the popularity of the method. Fetal asphyxia after PCB was first attributed to a high concentration of the anaesthetic in the fetal blood and direct depression of the circulation (Asling et al., 1970). However, bradycardia occurs even when the concentrations in the fetal blood are small (Liston, Adjepon-Yamoah and Scott, 1973). Local anaesthetics exert, both *in vitro* and *in vivo*, a vasoconstrictive effect on the uterine artery (Gibbs and Noel, 1976; Greiss, Still and Anderson, 1976; Morishima et al., 1976). The vasoconstrictive effect of mepivacaine, lignocaine, bupivacaine and chloroprocaine on the uterine artery is dose-related, but has been observed *in vitro* at blood concentrations which occur in clinical practice (Joyce, Aquino and Kuchling, 1976; Pue et al., 1977). In performing PCB (about 1000 times), the smallest concentration of lignocaine necessary to exert a vasoconstrictive effect *in vitro* is infiltrated close to the uterine artery.

Several precautions will increase the safety of PCB. Continuous fetal heart rate (FHR) monitoring before, during and after PCB is essential. Bloom, Horswill and Curet (1972) and Jägerhorn (1975) showed that an injection depth of only 2 mm (the thickness of the vaginal mucosa) is important for minimal intravascular spread of local anaesthetic. A careful and slow injection at four sites (4, 5, 7 and 8 o'clock) with a 3–5-min interval between injection of the two sides will reduce the risk of high blood concentrations. A small total dose of local anaesthetic will decrease the frequency of fetal bradycardia (Teramo and Widholm, 1967; Shnider and Gildea, 1973; Jägerhorn, 1975; Reisner et al., 1977). Neurobehavioural studies indicate the desirability of low doses also (Reisner et al., 1977). 2-chloroprocaine, an ester-type local anaesthetic which is rapidly hydrolysed in blood by plasma pseudocholinesterase, has a maternal and fetal half-life of 21 s and 43 s, respectively (Finster et al., 1974). Chloroprocaine 1%, used even with adrenaline

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1 : 200 000 which increases the frequency of fetal bradycardia, caused fetal bradycardia in only 5.8% of cases compared with 22% with either lignocaine or mepivacaine without adrenaline (Shnider and Gildea, 1973; Freeman and Arnold, 1975).

In spite of these fetal effects, PCB is still used by obstetricians in circumstances where lumbar extradural anaesthesia is not feasible. In skilful hands, used as described, and avoiding its use in prematurity, fetal distress and when delivery is expected within 1 h, PCB can be used relatively safely.

Pudendal nerve blockade (PNB)

PNB is an effective method of perineal analgesia which is popular with obstetricians for the second stage of labour. PNB eliminates pain in the lower portion of the vagina and in the perineum and permits low outlet forceps delivery and episiotomy. The transvaginal approach is technically simpler, less painful, has a higher success rate and there is less risk of damage to the fetus or to the rectum. However the failure rate in inexperienced hands is about 50% (Scudamore and Yates, 1966). The area of perineum anaesthetized is smaller and the quality of block poorer than in saddle block anaesthesia.

For forceps delivery it is advisable to combine inhalation analgesia with PNB (Gottschalk and Hamilton, 1973). The safest drug is chloroprocaine in 1.5–2% solution. When PNB is used, local infiltration is often essential and if PNB has been preceded by PCB, the maternal and fetal blood concentrations may be greater than those reported for extradural block for Caesarean section (Merkow et al., 1977).

Low spinal (saddle) block (SB)

This is popular in the U.S.A., where approximately half a million saddle blocks are performed annually. It is little used in Europe. Sacral roots 2–4 are anaesthetized in SB. This does not abolish the pain of uterine contraction. SB is induced when the cervix is dilated fully, immediately before spontaneous or operative vaginal delivery. The patient should be in the sitting position for 60 s after the injection before being placed in the lithotomy position. There is a rapid onset of intense analgesia with good relaxation of the muscles of the pelvic floor. This affords good anaesthesia for outlet forceps and repair of perineal and vaginal lacerations. So-called mid-cavity forceps or breech extraction require a higher level of spinal analgesia to T10. Arterial hypotension is rare in conjunction with SB, compared with a 10% frequency in so-called mid-spinal block (Moir, 1971).

SB may be used to supplement PCB in the second stage of labour. The advantages of SB are that it is technically easy and only small amounts of the analgesic drug are needed. The failure rate in practised hands is less than 1% (Albright, 1978). There are no risks of a drug effect on the infant. Although the frequency of hypotension in the mother is very low with SB, a preblock fluid load and proper positioning after the block are important. After injection of the anaesthetic the patient must be told to avoid straining during the uterine contractions so that the level of the block does not rise too high. The commonest and most unpleasant complication is headache, which is twice as common in parturient women as in non-pregnant women (Bonica, 1972). Therefore it is important to use a 25- or 26-gauge spinal needle, when the frequency of headache is generally less than 1% (Philips et al., 1969). Serious complications such as adhesive arachnoiditis and the cauda equina syndrome are very rare. Philips and his co-workers (1969) reported 10 440 spinal anaesthetics given to women in labour without any major complications.

EXTRADURAL ANALGESIA

The various techniques of continuous extradural analgesia currently used in obstetrics are:

(1) Caudal block (S5–T10).
(2) Lumbar extradural block (L2–T10 during the first stage and L2–S4 during the second stage).
(3) Double catheter technique (upper catheter for segmental block T12–T10 and lower catheter for sacral block S2–S4).

Caudal (sacral) analgesia

This was much favoured earlier in the U.S.A., but has been little used in Europe. Its popularity in the U.S.A. was because of excellent relaxation of the muscles of the pelvic floor and the reliable perineal anaesthesia produced by the technique; this is important when the delivery is to be completed with outlet forceps. Sacral anaesthesia obviates an urgent injection to obtain perineal anaesthesia immediately before delivery or to "top up" the block for the repair of an episiotomy. Also, the risk of puncturing the dura is less.

The reasons for the loss of popularity of sacral compared with lumbar extradural anaesthesia are:

a greater amount of anaesthetic is required, with an increased risk of maternal toxicity and fetal and neonatal depression
higher failure rate

slower onset

more risk of infection

risk of puncturing the patient's rectum or the head of the fetus

Lumbar extradural block

Technique and indications. Correctly administered, this offers many advantages over the other regional techniques. The anaesthetist can achieve specific blockade of pain pathways during each stage of labour without interfering with Ferguson's reflex and the internal rotation of the fetal head. It is possible at the beginning of the second stage of labour, using an analgesic concentration, to extend the blockade to the sacral segments to produce perineal analgesia. Once rotation of the fetal head has occurred greater concentrations may be used, at the end of the second stage of labour, to relax the muscles and facilitate controlled vaginal delivery.

The principal indication for extradural anaesthesia is maternal pain. The extradural technique is the only effective technique for pain relief in approximately 20% of all parturients who suffer intense pain. Moir and Willox (1967) found that, in 70% of the patients whose labour is protracted on account of incoordinate and hypertonic uterine contractions, extradural anaesthesia will improve the quality of uterine contractions and increase the rate of cervical dilatation. A special indication is toxaemia of pregnancy (Hansen and Ueland, 1966). There are preliminary data showing that the placental circulation of patients with toxaemia can be improved by extradural anaesthesia (Hollmén, 1978—personal communication). Extradural analgesia may prevent stress on the circulation in the patient whose cardiac reserve is limited and for whom a vaginal delivery is planned. Relaxation of the muscles of the pelvic floor and decreasing the pressure on the child's head in premature delivery reduces the risk of cerebral haemorrhage in the newborn (Ontario Perinatal Mortality Study Committee, 1967). Crawford (1975) reported that absolute contraindications in his practice are limited to situations in which either the patient does not want analgesia or she has a disturbance of the bleeding and coagulation system. The technique is now used in patients who have had a previous Caesarean section, in breech presentation and in multiple pregnancy, which earlier were considered as relative contraindications (Crawford, 1975).

Local anaesthetic. The popular local anaesthetic for extradural analgesia in obstetrics is bupivacaine. Its excellent sensory blockade, long duration of action, high plasma protein binding and minimal effects in the neonate, compared with the other amide-type local anaesthetics (Scanlon et al., 1976), all justify its use. During the early stage a 0.375% concentration of bupivacaine is most suitable for lumbar extradural analgesia. It provides intense sensory, but slight motor blockade. For anaesthesia, if an instrumental delivery is planned, a 0.5% solution is needed.

Chloroprocaine is now gaining popularity in the U.S.A. Its rapid onset and intense blockade, but especially its very low toxicity because of rapid hydrolysis in blood, make it both practical and safe (Freeman and Arnold, 1975; Marx, 1977). If necessary, the anaesthesia or analgesia may be stopped quickly. In the event of an intravascular injection the toxic symptoms disappear rapidly. Similarly, if a high spinal injection occurs, the effect passes off faster than when using bupivacaine. The usual concentration of chloroprocaine for pain relief at the stage of cervical dilatation is 2%. To combine the rapid onset and long duration "the Swedish–American cocktail" of 0.75% bupivacaine and 3% chloroprocaine yields 0.375% bupivacaine and 1.5% chloroprocaine. The use of this mixture is becoming popular for the first stage of labour. However, the controlled studies made have not confirmed that the combination achieves these advantages (De Campo et al., 1976). If extradural block is to be used for delivery only then is chloroprocaine preferable. Its brief duration avoids the need for catheterization of the bladder.

Failure of analgesia. The frequency of total failures with experienced anaesthetists is about 2% (Dawkins, 1969). Unilateral anaesthesia because of inadvertent catheterization of the anterolateral compartment of the extradural space is not rare (Caseby, 1974). In such cases, complete analgesia can be achieved by withdrawing the catheter about 2 cm and injecting a local anaesthetic with the patient lying on the unblocked side. Unblocked dermatome segments are encountered in 6–15% of lumbar extradural blocks (Ducrow, 1971; Crawford, 1972). Pulling the catheter outwards and asking the patient to lie on the unblocked side before giving the additional dose, perhaps a larger volume of a higher concentration of the local analgesic, can reduce the occurrence of an unblocked segment to about 1.5% (Ducrow, 1971). Pain in one groin becoming more severe as uterine concentrations become stronger may be caused either by the pulling of the round ligament and incomplete block of its nerve supply (T10–T8)

(Roberts, 1972; Albright, 1978) or by failure to block completely the largest spinal nerve root (S1) (De Campo et al., 1976).

Inadequate perineal anaesthesia in the second stage of labour is more frequent during lumbar extradural anaesthesia than are unblocked segments in the first stage. It occurs in spite of the injection of 12–15 ml of 3% chloroprocaine to the lumbar space for delivery with the patient in the semi-sitting position. If perineal anaesthesia is incomplete, attempts at its correction on the delivery table while the patient is in the lithotomy position are often unsatisfactory.

Effect on the course of labour. Although there are individual variations in the effects of extradural analgesia on uterine activity, the overall adverse effects of properly administered extradural analgesia are insignificant (Kandel, Spoerel and Kinch, 1966; Crawford, 1972).

In nulliparous women who have received lumbar extradural anaesthesia, the first stage may be shortened and the second prolonged because of perineal anaesthesia (Doughty, 1969; Crawford, 1972). Maternal hypotension which reduces uterine blood flow is the most common cause of decreased uterine activity and prolonged labour (Vasicka and Kretchmer, 1961). It has been suggested that the amide-type local anaesthetics may depress uterine activity directly (Lowensohn et al., 1974; Zadar and Nilsson, 1974). Low dose segmental extradural anaesthesia using bupivacaine 25 mg seems, however, not to depress uterine activity (Jouppila et al., 1977). To elucidate the effect of the segmental extradural technique on the duration of labour we studied groups of 100 patients undergoing extradural analgesia and 100 controls. The progress of labour before the induction of extradural blockade was slower in the extradural group. On the other hand, there were no differences between the groups in the duration of the first stage of labour after extradural anaesthesia (Jouppila et al., 1978b).

Adrenaline added to local anaesthetics in doses of 100 μg has been shown to slow labour significantly after extradural analgesia (Günther and Belvillè, 1972). Even as small a dose as 25 μg of adrenaline added to bupivacaine for segmental extradural analgesia decreases uterine activity for about 20–30 min (Jouppila et al., 1977). Its effect on prolonging the labour is, however, insignificant. The suggested mechanism is a beta-adrenergic stimulatory effect on the uterus.

The effect of extradural analgesia on the duration of the second stage of labour depends on the intensity of the perineal sensory block (Doughty, 1969). Using low-dose segmental extradural anaesthesia (T10–L1) and avoiding the delivery dose, the frequency of instrumental delivery is 4–5% (Hollmén et al., 1977). This concurs with the frequency in our control material (Hollmén, 1978—personal communication). Using the same extradural technique, the fetal malpositions at delivery are comparable to a control group (Jouppila et al., 1978b). If the perineum of primiparae is anaesthetized completely the instrumental delivery rate can be as high as 50% (Crawford, 1975).

Even when the perineum is well blocked, the mother who has no pain and is properly coached is often able to co-operate and push effectively, but the duration of the second stage of labour is lengthened by more than 50 min for primiparae (Crawford, 1972). The attitude to active shortening of the second stage (low outlet forceps or vacuum extraction) has diverged in the U.S.A. and Europe. The frequency of spontaneous vaginal deliveries seems to be growing today in the U.S.A., whereas a more positive view is being taken in Europe (for example, in Britain and the Scandinavian countries) to active acceleration of the second stage of labour in connection with extradural analgesia. The latter development is positive as the prolongation of the second stage of labour will increase the metabolic acidosis of the newborn (Zador and Nilsson, 1974).

Effect on uterine blood flow. Uterine blood flow is of great importance to fetal wellbeing. Although a healthy fetus tolerates well a 20–50% short-lived reduction in placental blood flow (Greiss, 1973), any reduction in uterine blood flow caused by an analgesic technique will be a negative aspect of that technique.

The presently available scanty data on the effects of extradural analgesia upon uterine and placental blood flow seem to indicate that this technique will not change the uterine blood flow in healthy parturients in labour, provided hypotension is avoided (Brotanek et al., 1973; Jouppila et al., 1978a). Hypotension is, however, the most common complication of extradural analgesia, its frequency varying from 1.4 to 13.0%, depending on the preventive steps (rapid preloading with infusion of crystalloids and left lateral tilt) and the patient, as well as the criteria used to define hypotension (Crawford, 1972; Aronski et al., 1973). Dehydration and narcotics given during early labour will increase the tendency to hypotension (Crawford, 1975). Using low-dose segmental (T10–L1) extradural anaesthesia in 418 parturients, Hollmén and colleagues (1977) found a 16.5% frequency of hypotension when the preventive steps were not used. With the same technique in another series of 427 parturients (Hollmén, 1978—personal communication) where both preload and lateral tilt or lateral position were routinely used, the frequency of hypotension was 6.6%.

An i.v. infusion of adrenaline 50–100 μg per 5 min in pregnant ewes caused a 38.5% decrease of uterine blood flow (Rosenfeld, Barton and Meschia, 1976) and adrenaline 60 μg added to chloroprocaine and given via the extradural route to pregnant ewes caused at 14% decrease in uterine flow (Wallis et al., 1976). We have shown in parturients that adrenaline 20 μg used with low-dose bupivacaine for segmental extradural block has no effect on placental blood flow. However, extradural blockade using a dose of adrenaline 80–100 μg with lignocaine for Caesarean section anaesthesia decreases the placental blood flow by 13% (Jouppila et al., 1978c).

Uterine vessels constrict when exposed to high concentrations of local anaesthetics (Cibils, 1976; Gibbs and Noel, 1976). Greiss, Still and Anderson (1976) infused local anaesthetics into the uterine artery of non-pregnant ewes and measured a 40% reduction of mean uterine blood flow when the arterial concentration of bupivacaine was 5 $\mu g\ ml^{-1}$. Morishima and colleagues (1976), using lignocaine infusion, produced blood concentrations of lignocaine 4–9 $\mu g\ ml^{-1}$ and reported a reduction of uterine blood flow. In clinical practice the plasma concentrations of local anaesthetics are considerably smaller than this. When clinically encountered plasma concentrations of lignocaine or chloroprocaine were studied in pregnant ewes, there was no reduction of uteroplacental blood flow (Wallis et al., 1976; Biehl et al., 1977). We observed no decrease in the placental blood flow when using a small dose of bupivacaine for a segmental extradural analgesia in normal parturients (Jouppila et al., 1978a). With this technique the maternal plasma bupivacaine concentration is about 0.2 $\mu g\ ml^{-1}$ (Hollmén, 1970). Extradural analgesia has been specially advocated for toxaemia, but the placental blood flow is reduced in toxaemia (Käär et al., 1977). Our preliminary data of studies in progress at Oulu University Hospital show that the segmental extradural block seems to improve placental blood flow (R. Jouppila, 1978—unpublished observations).

Effect on fetal heart rate. The reported frequency of fetal heart rate (FHR) changes after extradural analgesia varies greatly (Zilianti et al., 1970; Maltau, 1975; Raabe and Belfrage, 1976). When hypotension occurs combined with the use of oxytocin, the frequency of FHR changes can be as great as 40% (Schifrin, 1972). Late deceleration changes have been shown to increase more than five-fold when the supine instead of the lateral position is used (Huovinen, Kivalo and Teramo, 1976). Using a small dose of bupivacaine for segmental extradural analgesia in a series of 105 parturients, Jouppila and colleagues (1977) found only a 9% frequency of pathological FHR changes. In this series left lateral tilt was maintained constantly after the block. In their series 35% of these FHR changes occurred in connection with maternal hypotension.

It may be concluded that, properly administered extradural analgesia does not produce pathological FHR changes. Obvious pathological changes in FHR after lumbar extradural anaesthesia are almost always associated with maternal hypotension, the supine position, the use of oxytocin and uterine hypertonia.

Double-catheter technique

High segmental extradural technique (*T10–T12*). During the first stage of labour a catheter is placed in the extradural space at the level of T11 and 4 ml of bupivacaine 0.5% is injected. We have used this technique in approximately 1500 patients at the Central Hospital, University of Oulu (Hollmén et al., 1977). Good analgesia for the first stage of labour has been achieved in 96% of patients.

In our series about 90% of the deliveries of primiparae ended with spontaneous delivery after a second stage lasting less than 30 min. The acid–base balances of the mother, fetus and the newborn were comparable to those at other centres using lumbar extradural analgesia (Hollmén, 1970; Zador and Nilsson, 1974).

Sacral anaesthesia (*S2–S4*). Effective analgesia during the second stage is achieved by placing a second catheter in the sacral space in the "latent phase" of delivery and injecting through it at the beginning of the second stage an analgesic solution such as 5 ml of 0.25% bupivacaine. When flexion and rotation of the fetal head are complete, an anaesthetic dose of chloroprocaine 3% is injected. This produces relaxation of the perineal muscles and facilitates the delivery of the baby whether spontaneous or assisted.

Generally, with the double-catheter technique, analgesia is both faster and more adequate compared with lumbar extradural analgesia. As less local analgesic is used in the double-catheter technique, the

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maternal, fetal and neonatal plasma concentrations are less than with the lumbar extradural technique. The double-catheter technique obviates the necessity of positioning the mother before administering the dose for delivery and ensures better perineal anaesthesia than with the lumbar extradural technique. Maternal hypotension and other side-effects are less likely. Although proposed by Cleland in 1952, the use of this technique today is limited in spite of the advantages it offers. It is used primarily in special cases of high risk such as patients with diabetes, toxaemia or heart disease.

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DISCUSSION

Dr Bonica: I am worried by how often the results of laboratory experiments done *in vitro* are extrapolated into the clinical situation. Isolated strips of myometrium and uterine blood vessels are often exposed to enormously high doses of local anaesthetics and the deleterious effects which ensue sometimes discourage the use of local anaesthetic techniques in obstetrics. We must be prepared as clinicians to point out that the intact uterus during labour is quite different from an isolated strip in the laboratory.

Could I also raise the question of manpower, particularly anaesthetic manpower in obstetric analgesia. It seems quite wrong that we are prepared to give a great deal of time to such things as cardiac surgery and so little time to the management of labouring women. A mother and her baby represent many years of future useful life and yet our resources are often diverted towards patients whose prognosis in terms of active life is extremely limited.

Dr Finster: Could I also emphasize the fallibility of extrapolating from laboratory and animal models to man. For example, you showed data regarding chloroprocaine in sheep. Chloroprocaine, being an ester, is metabolized in the human by being hydrolysed by plasma cholinesterase. The sheep, unlike man, has practically no cholinesterase activity in its blood and chloroprocaine will be a very much more toxic agent in the sheep than in man.

Dr Rosen: I would like to emphasize the question of manpower in obstetric anaesthesia. In the United Kingdom we need a considerable increase in the number if we are to give proper service in regard to obstetric analgesia.

Dr D. B. Scott (Edinburgh): Recently we carried out a survey into the number of obstetric anaesthetic sessions in the United Kingdom and found that on average less than 1 session per week is devoted to 1000 deliveries a year. In other words a unit with 4000 deliveries a year has on average less than 4 half-days per week given to obstetric anaesthesia. Training is also deficient, and it is surprising that we turn out anaesthetists all of whom are quite capable of conducting anaesthesia for open heart surgery, but are unable properly to perform extradural block in labour.

Dr J. P. Gauthier-Lafaye (Strasbourg): To achieve a major breakthrough in introducing local anaesthetic techniques to patients in labour in France, we must first convince our obstetric colleagues of the advantages of the method. Second, when local anaesthetic techniques are carried out it is very important that they are given by skilled anaesthetists properly trained in the methods.

Dr Bonica: Once you start achieving success with obstetric analgesia, women themselves will demand proper pain relief from their obstetricians and help to change attitudes. It is inconceivable to me that anybody calling himself a trained anaesthetist should be incapable of carrying out local anaesthetic techniques.

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PLACENTAL TRANSFER AND FETAL UPTAKE OF DRUGS

M. Finster and H. Pedersen

The passage of drugs across the placenta and their distribution into and ultimate removal from fetal tissues are influenced by a variety of factors. Of prime significance are the physicochemical properties of the compound in question. Equally important, however, are the pertinent anatomical features of the maternal circulation, the placenta and the fetus, as well as haemodynamic and pharmacokinetic events within them.

PHYSICOCHEMICAL PROPERTIES

Foreign organic substances penetrate most cells as though the boundary had the characteristics of a lipoid membrane (Brodie, Kurtz and Shanker, 1960). Such a membrane is almost impenetrable by charged or ionized molecules, but is relatively permeable to un-ionized molecules whose rate of transfer depends upon their lipid solubility.

It was held formerly that neuromuscular blocking drugs could not cross the placenta in significant amounts because of their high degree of ionization and low lipid solubility. However, recently developed sensitive and specific analytical techniques show measurable, albeit low, concentrations of tubocurarine in blood specimens taken from the umbilical vessels at delivery, even following the use of clinical doses (Pedersen and Finster, unpublished data). Similarly, studies on Rhesus monkeys, have shown placental transmission of suxamethonium to be more rapid and extensive than previously believed (Drábková, Crul and van der Kleijn, 1973). In humans, suxamethonium given to a mother with atypical serum cholinesterase can cause neonatal flaccidity and apnoea in atypical homozygous infants. Heterozygous infants do not seem to be seriously affected (Baraka et al., 1975).

The proportion of a drug in the uncharged and charged forms is given in the same form as the Henderson–Hasselbalch equation:

$$pH = pKa + \log [base]/[cation]$$

In the case of local anaesthetics, this ratio is of pharmacological importance, since it is the base which is believed to penetrate the tissue diffusion barriers, while the cation is considered to block conduction when in direct contact with the nervous tissue. Commonly used local anaesthetics have pKa values ranging from 7.7 to 9.1. These values are sufficiently close to the blood pH so that maternal or fetal acid–base imbalance should result in significant changes in the ratio of ionized to un-ionized fractions of the drug. Thus, for example, in the acidotic fetus the proportion of ionized drug is greater than in the healthy fetus. With equal blood concentrations of the un-ionized moiety (which is in equilibrium with that of the mother), the total blood concentration of a local anaesthetic in the acidotic fetus will be greater than in the healthy one. This has been demonstrated both clinically and experimentally (Biehl et al., 1976; Brown, Bell and Alper, 1976). Fetal acidosis should have similar effects on other basic drugs, such as pethidine and morphine.

Molecular size is also important. Assuming adequate lipid solubility, most un-ionized drugs of molecular weight less than 500 cross cell boundaries readily, while most of those with molecular weight exceeding 1000 do not cross at all.

Anaesthetic agents in the maternal circulation traverse the placenta by simple diffusion, a process governed by mainly physicochemical factors, in accordance with Fick's law. The rate of diffusion is directly proportional to the concentration gradient of the substance between maternal and fetal blood, and the surface available for transfer, while it is inversely proportional to the thickness of the membrane.

Factors affecting maternal blood concentrations of drugs

These include: the total dose, the site and mode of administration, and the rate of metabolism and

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excretion. The well-known swift decline of drug concentrations in the plasma following the i.v. injection of thiopentone results in a correspondingly short time of exposure of the uterine contents to high blood concentrations of this drug (Finster et al., 1966; Kosaka, Takahashi and Mark, 1969). In contrast, the maintenance of anaesthetic concentrations of the various inhalation agents administered to the mother is associated with continuing transfer of drug to the fetus (Siker et al., 1968; Marx, Joshi and Orkin, 1970).

All amide-linked local anaesthetic agents have been detected in the maternal blood within minutes of administration. Mepivacaine reaches peak concentrations in maternal blood within 25–40 min following a single extradural injection (Morishima et al., 1966). The decrease which follows is sufficiently slow to account for maternal (and fetal) accumulation after repeat injections. Similar effects were noted when mepivacaine was used for continuous caudal analgesia (Moore et al., 1968). Absorption of local anaesthetics from the paracervical area appears to be more rapid than from the extradural space, because of greater vascularity of the area, maternal drug concentrations reaching the maximum values within 9–10 min of injection (Petrie et al., 1974).

This maternal accumulation may be reduced by the use of long-acting local anaesthetics, such as bupivacaine or etidocaine, which require less frequent repeat injection, or by the use of rapidly metabolized drugs. No measurable maternal blood concentrations have been demonstrated following the use of chloroprocaine, an ester, which is hydrolysed by plasma pseudocholinesterase ($T_{\frac{1}{2}} = 21$ s) (Finster et al., 1973). Metabolism of the drug was noted even in plasma samples obtained from subjects with homozygous atypical cholinesterase, although at a slower rate ($T_{\frac{1}{2}} = 106$ s).

ANATOMICAL AND HAEMODYNAMIC FACTORS

The uterine blood flow increases steadily throughout pregnancy, reaching an average value of 500–700 ml min^{-1} (approximately 10% of the resting cardiac output) in the human female at term. About 80% of this flow reaches the placenta; the remaining 20% perfuses the uterine muscle and endometrium. Reduction in utero–placental blood flow, from whatever cause, will result in decreased delivery of the drug to the fetus. This may occur during maternal arterial hypotension associated with regional analgesia, aorto-caval compression or haemorrhage, or in chronic conditions such as toxaemia and diabetes.

On the fetal side of the placenta, the umbilical flow, estimated at 600 ml min^{-1}, represents at least 50% of the combined fetal cardiac output.

The relative directions of maternal and fetal blood flows within the placenta may affect the efficiency of transfer of respiratory gases, drugs and other substances between mother and fetus. In the human placenta, these exchanges appear to be based on a "multivillous stream" vascular pattern, in which maternal blood, as it traverses the intervillous space, flows successively past a large number of fetal villi. As oxygen from the maternal stream enters the fetal blood, fetal capillaries lying further downstream in the intervillous space are exposed to maternal blood of progressively decreasing oxygen tension. A comparable reduction in the concentration of drugs in the maternal blood stream is to be expected also.

Oxygen, nutrients and drugs are carried to the fetus by the umbilical vein. Cord compression, which occurs in at least one-third of vaginal deliveries, may diminish transfer of all of these substances to the fetus. A variable proportion of the umbilical vein blood perfuses the fetal liver and enters the inferior vena cava through the hepatic vein, while the remainder is shunted through the ductus venosus directly into the inferior vena cava. Consequently, a portion of any drug is strained through the liver before gaining access to the rest of the fetus. Furthermore, the drug undergoes dilution during its transit to the arterial side of the fetal circulation, as blood in the umbilical vein mixes with fetal venous blood from the gastrointestinal tract, from the lower extremities, from the head and upper extremities, and from the lungs. This unique pattern of the fetal circulation results in a delay in equilibration between fetal tissues and fetal blood, manifested by the persistent gradient in drug concentrations between the umbilical vein and the umbilical artery. This has been demonstrated for a variety of anaesthetics, including thiopentone (Finster et al., 1966), lignocaine (Shnider and Way, 1968) and nitrous oxide (Marx, Joshi and Orkin, 1970). Furthermore, the greater the tissue solubility of an anaesthetic, the slower the increase in the umbilical artery concentration (Marx, 1973).

The distribution of the fetal cardiac output may be altered by fetal hypoxaemia and, even more, by a combination of hypoxaemia and acidosis (Cohn et al., 1974). Under these conditions, blood flow to the placenta, and to the fetal brain, heart and adrenals, increases substantially, while perfusion of the lungs, kidneys, spleen, gut and carcass diminishes. Drug distribution in fetal tissues should follow similar patterns.

FACTORS AFFECTING FETAL TISSUE UPTAKE

Placenta

Uptake and metabolism of drugs by the placenta, if they occurred, would decrease the amount transferred to the fetus. Studies with several anaesthetic agents, such as halothane and lignocaine, have shown limited uptake by this organ (Finster et al., 1972; Geddes et al., 1972). Placental metabolism *in vivo* has not been reported for any analgesic or anaesthetic commonly used in obstetric practice.

Fetus

Any drug transferred across the placenta is carried to fetal tissues, where its uptake depends on the tissue/blood partition coefficient of the drug and the tissue perfusion. Uptake of lignocaine in fetal tissues was studied in pregnant guineapigs following i.v. injection into the mother (Finster et al., 1972a). Relatively high concentrations were found in fetal liver, myocardium and brain, demonstrating the rapid distribution to highly perfused fetal organs. The liver was the only organ in which lignocaine concentrations in the fetus exceeded those in the mother. Substantial hepatic accumulation of other anaesthetic drugs such as thiopentone (Finster et al., 1972b) and halothane (Geddes et al., 1972) has been shown. The strategic situation of the fetal liver in regard to the umbilical circulation has been mentioned already.

The importance of lipid solubility in the fetal tissue uptake of local anaesthetics has been demonstrated recently in a study comparing the placental transfer of several local anaesthetics in pregnant guineapigs (Morishima et al., 1975). The ratio of etidocaine or bupivacaine concentration between the fetal and maternal blood was substantially less than that found for lignocaine. This observation was in agreement with data on the umbilical vein/maternal blood concentration ratio (UV/M) computed in human studies (Covino, 1971). However, the proportion of the injected dose recovered from fetuses over the first 60 min was remarkably similar for all three drugs studied. In contrast, the uptake of etidocaine or bupivacaine in the fetal myocardium, brain and liver was substantially greater than for lignocaine. These relatively high tissue concentrations of the long-acting agents in the fetus relate to the fact that bupivacaine is approximately 10 times, and etidocaine 50 times, more soluble in lipids than is lignocaine. High protein binding of bupivacaine and etidocaine (which in guineapigs is similar to that in humans) failed to limit their placental transfer. The relatively small fetal blood concentrations of these drugs can be explained on the basis of greater tissue uptake.

The effects of asphyxia on the fetal circulation and on the accumulation of anaesthetic bases in the blood of an acidotic fetus, secondary to increased ionization of drug, have already been discussed. Similarly, tissue acidosis in the fetus may enhance drug transfer into organs such as the heart and brain.

METABOLISM AND EXCRETION IN THE FETUS AND NEWBORN

Experimental data gathered over the past few years indicate that the fetus and the newborn are capable of metabolizing and excreting certain local anaesthetics. For example, in plasma samples obtained from the umbilical vessels at birth, chloroprocaine was rapidly hydrolysed, the half-life being approximately 43 s (Finster et al., 1973). Although the human fetal liver at term contains microsomal enzymes capable of metabolizing amide local anaesthetics, there is no direct evidence, at present, of the metabolism of these drugs by the human fetus. The human newborn has been shown to eliminate lignocaine and mepivacaine in its urine, the former mostly as metabolites (Meffin, Long and Thomas, 1973; Blankenbaker, DiFazio and Berry, 1975). Measurements of plasma half-lives in the human newborn have shown them to be 3 h for lignocaine, 9 h for mepivacaine and 2 h for bupivacaine (Brown et al., 1975; Ralston and Shnider, 1978). Our detailed pharmacokinetic study of lignocaine in fetal and newborn lambs and adult sheep indicates that the metabolic clearance in the newborn is quite similar to, and renal clearance greater, than in the adult (Morishima et al., 1979). Nonetheless, the elimination half-life is more prolonged in the newborn. This is because of a greater volume of distribution and tissue uptake of the drug, the result being that at any given time the neonate's kidneys are exposed to a smaller fraction of the lignocaine accumulated in the body. The renal excretion of mepivacaine has been documented in human fetuses (Brown et al., 1977) and is believed to be responsible for most of the drug in the amniotic fluid. Since the fetus swallows amniotic fluid periodically, re-uptake of the drug into the fetal circulation may take place by this route.

SUMMARY

Practically all drugs used in obstetric anaesthesia cross the placenta by simple diffusion according to the concentration gradient. Factors governing this process are: lipid solubility, degree of ionization, molecular weight. Equilibration within

the fetus is affected by uptake by the liver and by consecutive dilution in the venous side of the fetal circulation. Recent data indicate that the fetus and the newborn are capable of metabolizing and excreting certain local anaesthetic agents.

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METABOLISM OF LOCAL ANAESTHETICS IN THE FETUS, NEWBORN AND ADULT

C. A. DiFazio

Because of their relatively low molecular weight (less than 500) and because they have a lipid-soluble un-ionized component, local analgesics can freely pass in either direction through the placenta. Therefore, it is not surprising that substantial quantities administered to the mother before delivery are to be found in the newborn after delivery. The actual amount of drug passed from the mother to the fetus is determined by the plasma concentration of free drug (considered equal in mother and fetus), the tissue/plasma partition coefficient of the free drug in the fetus and blood flow to that tissue. Therefore each compartment (blood or tissue) accumulates drug and acts as a reservoir for the drug. The size of the reservoir of each drug is determined by tissue binding and solubility. The metabolism of the drugs by both mother and fetus will, in turn, affect the amount of drug remaining in the newborn after delivery.

Disposition of drug

Metabolism or biotransformation of drugs terminates the activity of pharmacologically active chemicals and facilitates their excretion. Most drugs when present in the non-polar, lipid-soluble state can penetrate membranes to produce a cellular response, and are reabsorbed in the renal tubule in this state. For local anaesthetics, renal excretion of the parent compound is small, usually constituting only 5–10% of the administered dose. These drugs must undergo biochemical reactions to convert them into more polar, water-soluble compounds so that they may be excreted readily. For ester-type local anaesthetics, degradation occurs in plasma by maternal pseudocholinesterase, and conversion of the parent drug into inactive polar compounds prevents accumulation in mother and fetus. For local anaesthetics of the amide type, biotransformation occurs primarily in the liver, utilizing the hepatic microsomal drug-metabolizing system of the endoplasmic reticulum. This enzyme system is capable of carrying out a variety of reactions including dealkylation, oxidation (hydroxylation), hydrolysis and conjugation (fig. 1). Many drugs, including local anaesthetics, are seen to undergo several reactions before being cleared from the body.

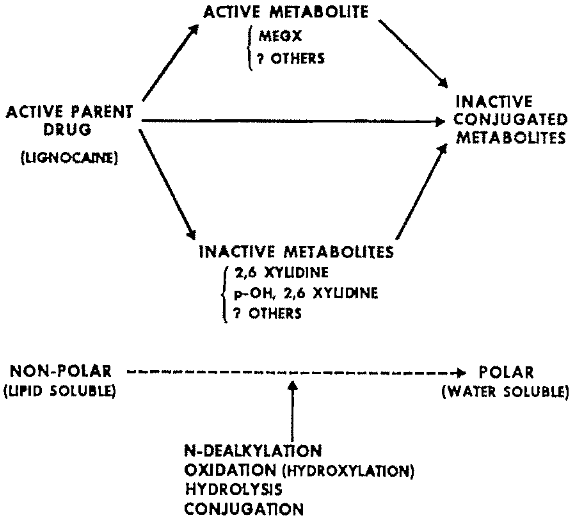

FIG. 1. A scheme for the biotransformation of active, non-polar drugs to inactive, polar, excretable substances is shown. Lignocaine is used to illustrate the reactions common to local anaesthetic agents.

The metabolism of lignocaine is an example of drug biotransformation where all the reactions mentioned above are seen in the conversion from a non-polar active drug to a polar metabolite that can be readily excreted.

The observations that newborn mice and guinea-pigs (Jondorf, Maickel and Brodie, 1958), and newborn rats and rabbits (Fouts and Hart, 1965; Henderson, 1971) could not carry out N-dealkylation, oxidations or glucuronide conjugation, lead to the assumption that the human newborn would not metabolize drugs, and thus would be more likely to suffer toxic effects from drugs received during birth by placental transmission or by drugs administered in the period after birth. However, the human

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neonate was found to be capable of numerous reactions including oxidation and dealkylation. Concentrations of cytochrome P450 and NADPH–cytochrome c reductase activity were found to be about 85% of the adult concentrations (Ackerman, Rane and Ericsson, 1972). The newborn is capable of conjugation reactions with glycine and glucuronic acid (Vest and Salzberg, 1968). However, a limited capacity of the neonatal UDP–glycuronyl transferase system is suggested by zero-order saturation kinetics observed with phenobarbitone and diphenyl hydantoin (Jalling et al., 1973). Further discussions of enzyme competence in the newborn can be found in several reviews (Mirkin, 1975; Dodson, 1976; Horning et al., 1976).

Adult and infant metabolism

Lignocaine. Metabolism of amide-type local anaesthetics in the adult involves a number of reactions. The structures and amounts of the local anaesthetic drugs used commonly in obstetrics, and each of the metabolites excreted, are shown in figure 2. Lignocaine undergoes principally N-dealkylation, hydrolysis and ring hydroxylation (oxidation) before conjugation and excretion. The oxidative dealkylation of lignocaine to monoethylglycine xylidide (MEGX) is the principal pathway, with MEGX being only slightly less potent and less toxic than lignocaine (Blumer, Strong and Atkinson, 1973). The usual concentrations of MEGX in plasma after lignocaine administration has been reported to be one-sixth to one-half the concentration of lignocaine in both man and animals (DiFazio and Brown, 1971; Strong, Parker and Atkinson, 1973; Blankenbaker, DiFazio and Berry, 1975). Amide hydrolysis of MEGX leads to the formation of inactive xylidine and subsequently to inactive p-hydroxy xylidine. Amide hydrolysis of MEGX is extensive. Beckett, Boyes and Appleton (1966) observed that only 12% of a dose of MEGX administered to volunteers appeared in the urine. Further dealkylation of MEGX to glycine xylidide (GX) has been observed in man (Strong, Parker and Atkinson, 1973) and animals (DiFazio and Brown, 1971) after constant i.v. infusion. This metabolite is considerably less potent (one-tenth) than the parent compound. Formation and excretion of very small

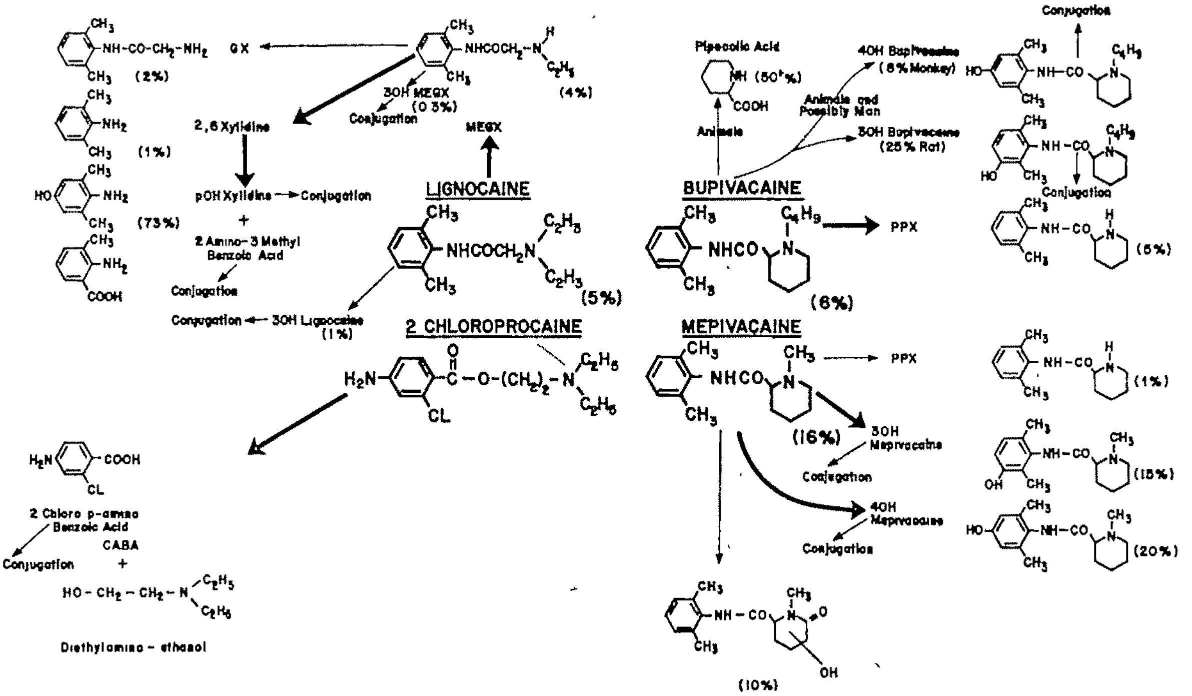

FIG. 2. The chemical reactions involved in the metabolism of local analgesics commonly used in obstetrics are shown. The number in the parentheses represents the percentage of an administered dose of each drug that is excreted in the form shown.

amounts of 3-hydroxy-lignocaine and 3-hydroxy-MEGX have been reported after oral administration of lignocaine (Keenaghan and Boyes, 1972).

The newborn infant has the capacity to metabolize lignocaine in a manner similar to that in the adult. Measuring urinary excretion of lignocaine and metabolites, Blankenbaker, DiFazio and Berry (1975) found a considerable increase in the metabolites of lignocaine at 12–24 h after birth. The serum half-life of lignocaine in the newborn is, however, longer than in the adult (Brown et al., 1975), namely 3 h for the newborn and 1.6 h for the adult. This would indicate that, while metabolic pathways in the newborn are similar, the rates of metabolism are reduced when compared with the adult.

Mepivacaine. The metabolism of mepivacaine, another amide-linked local anaesthetic agent (fig. 2) used commonly in obstetrics, has been studied in the adult and newborn. In the adult, both dealkylation and hydroxylation (oxidation) reaction are seen. Thomas and Meffin (1972) and Meffin and colleagues (1973) have reported that in the adult only 1% of the drug is excreted as the dealkylated metabolite pipecolylxylidine (PPX). Ring hydroxylation occurs as the primary reaction and results in the excretion of 15–20% of the drug as 3-hydroxy mepivacaine and 10–14% as 4-hydroxy mepivacaine. These metabolites are subsequently conjugated and excreted in urine. It is interesting to note that mepivacaine has two stereospecific isomers. The D(+) isomer is about twice as active as the L(−) isomer (Ludvena, Bogado and Tullar, 1972) and since the drug in clinical use is the racemic mixture, the site of hydroxylation (3–4 position) may be the result of a specific isomer reaction.

In the human newborn, Meffin, Long and Thomas (1973) observed that the metabolism of mepivacaine was markedly slower as compared with that of the normal adult. The newborn was unable to produce significant quantities of the ring hydroxylated metabolites of mepivacaine and had to depend mainly on renal excretion as the primary mode of clearance. Since renal excretion of local anaesthetics is considerably slower, it is not surprising that the half-life of mepivacaine in the newborn was found to be 9 h (Brown et al., 1975), about five times that in the adult.

Bupivacaine. Bupivacaine is another of the amide local anaesthetics used commonly. Structurally, this drug closely resembles mepivacaine, differing only in the N-alkyl group on the piperidine nitrogen (fig. 2). Such a structural change increases potency, lipid-solubility and protein binding of the drug. The metabolism of bupivacaine in man (Reynolds, 1971) occurs by N-dealkylation to PPX (fig. 2). This pathway is little used with the shorter alkyl group of mepivacaine. PPX is about one-eighth as potent and as toxic as the parent compound, and is mainly excreted in urine. In normal subjects who received PPX, approximately 50% was recovered unchanged in the urine. This substantiates the impression that both bupivacaine and PPX are resistant to amide hydrolysis in man. While ring hydroxylation is a common pathway in animals, it is not a major pathway in man. In animals hydrolysis and oxidation reactions are common (fig. 2), producing pipecolic acid and the 3-hydroxy and 4-hydroxy derivatives of bupivacaine (Goehl, Davenport and Stanley, 1973). In man, only one report of trace amounts of an unidentified glucuronide, of a possible hydroxy derivative, has been noted in patients receiving bupivacaine (Reynolds, 1971).

In the newborn, little urinary excretion of bupivacaine occurs; however, the N-dealkylated PPX begins to appear at about 12 h and reaches a peak concentration in 24 h in the urine (Ostheimer et al., 1974). Thus the infant, like the adult, uses a dealkylating mechanism of detoxification. With mepivacaine, the N-alkyl substitution was a shorter chain, and this pathway was not used in the newborn metabolism of mepivacaine. The half-life of bupivacaine in the infant may be prolonged also. While the adult half-life is reported as 2–3 h, that seen in the infant may be as long as 9 h (Belfrege et al., 1975).

The recovery of only small amounts of an administered dose of bupivacaine, as either parent compound or metabolite, may in part reflect difficulties in analytical techniques. The concentrations of bupivacaine and its metabolite become so small within hours of administration as to cause a problem of identification. It may be that other excretory pathways need to be evaluated. Is this highly lipid-soluble drug excreted via bile or faeces ? Further, analysis of tissue concentrations of the drug with time would help to identify the role of this reservoir in the total scheme of bupivacaine storage.

The metabolism of the local anaesthetics in the fetus should be considered also. Before birth drugs pass from the placenta to the fetal liver and to the fetal circulation via the ductus venosus to produce equilibrium with all fetal tissues (fig. 3). Part of the blood flow from the placenta enters the fetal liver via the portal vein where binding, and some metabolism, occur. The metabolites formed by the fetus can be

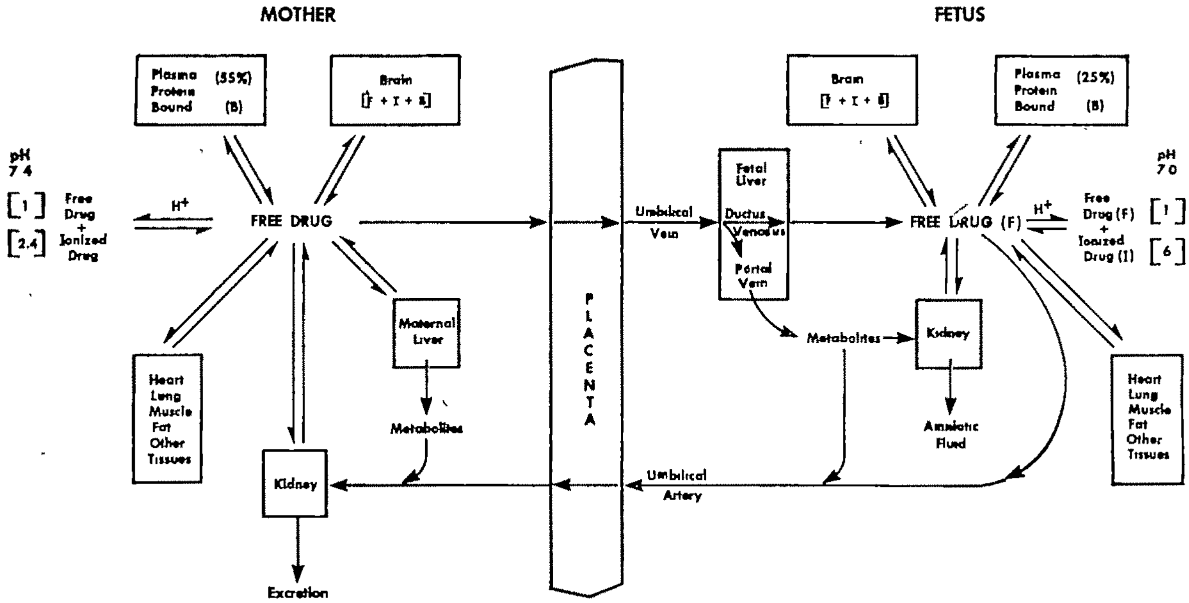

FIG. 3. A diagrammatic representation of the distribution and metabolism of drugs in the maternal–infant unit. The numbers shown in parentheses represent values that can be seen in mother and fetus with lignocaine.

either excreted into the amniotic fluid via the fetal kidney or passed back into the maternal circulation to be excreted by the maternal kidney. Since the maternal mechanisms are more mature and active than those of the fetus, the reduction in free drug concentration in both mother and fetus will be limited primarily by the maternal rate of metabolism. Even if the drug is administered to the fetus accidentally, it will traverse the placenta rapidly and undergo biotransformation in the mother. When maternal, fetal and newborn lignocaine concentrations were observed in sheep (Morishima et al., 1975), the rate of disappearance of drug in the mother and fetus was the same and was greater than in the newborn.

In conclusion, the fetus seems to clear most local anaesthetics well, with the mother providing the mature enzyme systems for metabolism and excretion. Once separated from the mother, the newborn is metabolically capable of carrying out the biotransformation of local anaesthetics, but a small delay in metabolism and excretion is observed, with the half-life of mepivacaine most prolonged.

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DISCUSSION

Dr Scott: Dr Finster has shown that in man the breakdown of chloroprocaine is extremely rapid, but Dr DiFazio, showing the slide of the study by Raj and colleagues, seemed to indicate that rather high plasma concentrations were achieved for a substantial time. Would Dr Finster please comment on this?

Dr Finster: We believe that the explanation for this lies with the analytical technique used by Raj and colleagues. Their method does not differentiate between the parent compound and its metabolites. When more specific analysis is used, chloroprocaine disappears very rapidly from human blood and there is a rapid build-up of metabolites.

Dr Rosen: I would like to offer an explanation in Dr Finster's experiments with placental transfer of pethidine for the differences between i.v. and i.m. administration. In experiments we have carried out in human adults, there were very big differences in the plasma concentrations using the two methods. I.v. injection, of course, gives an immediate high concentration whereas it takes about 45 min to achieve a peak concentration with the i.m. route and that peak concentration is much lower. I therefore think that if you had extended your experimental time you would have found that the concentration plots would have crossed. Regarding the excretion of pethidine, we have found that it takes approximately 67 h to achieve 95% elimination in the neonate (Hogg et al., 1977). In neonates the rate of conversion of pethidine to norpethidine takes twice as long as in the adult.

Dr Finster: Yes, we are hoping to extend our studies to see if in the course of time the plasma concentrations in the fetus do tend to equalize between the methods of administration, or even reverse. We are also looking at the question of uptake into tissues, particularly the brain, the liver and the myocardium.

Dr A. Hollmén (Oulu): Regarding the placental transfer of local anaesthetics in your guineapig experiments, did you measure the pH of the fetus because when we carried out studies of a similar nature in rabbits (Hollmén, 1973) we found that some of the fetuses were much more acidotic than others and this may well have an influence on the amount of drug being transferred.

Dr Finster: Unfortunately all our animals were studied after death, induced by freezing in liquid nitrogen, and it is therefore impossible to extrapolate their pH back to the moment of death.

Dr C. A. DiFazio (Charlottesville): As mentioned by Dr Hollmén, it has been shown with bupivacaine that, with an acidotic fetus (rabbits), there is an increase in drug tissue concentrations, in all tissues except fat (Sjostrand and Widman, 1973).

Dr Finster: Regarding the excretion of lignocaine, Dr DiFazio claimed that only 5% is excreted unchanged in the urine. This, of course, must refer to the adult only. In the human fetus it is impossible to tell because we do not know the exact quantity of drug that has reached the fetus; in animal experiments we have shown that up to 17% may be excreted unchanged in the neonate's urine.

Dr DiFazio: Of course, without knowing the dose of drug that the fetus has received, it is impossible to tell what proportion is excreted unchanged. However, the quantities found in the urine in the first 24 h after birth were very small (Blankenbaker, DiFazio and Berry, 1975).

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NEUROBEHAVIOURAL EFFECTS OF OBSTETRIC ANALGESIA

G. W. OSTHEIMER

The use of regional anaesthetic techniques for the relief of pain in childbirth continues to increase in North America and Europe. After the enthusiastic initial acceptance of a therapeutic programme that left the mother awake and co-operative instead of drugged and "at risk" from a variety of problems including aspiration pneumonitis, interest has turned to the effect of these drugs on the newborn.

Neurobehavioural assessment, a new tool in human clinical pharmacology, has suggested that many drugs previously thought to be without effect on the newborn do, in fact, have the capability to alter behavioural and adaptive functions.

The purpose of this review is to bring the current information in this rapidly expanding field up to date and project what benefits may accrue from neurobehavioural testing in the future.

HISTORY

The concept that childbirth must be a painful experience can be traced back to the Old Testament. In *Genesis*, Chapter III, verse 16, the Lord said to Eve: "I will greatly multiply thy pain and thy travail, in pain, thou shalt bring forth children...." This passage was interpreted so literally in some areas that in Edinburgh in 1591, Eufame MacAlyane was burned alive at the stake for seeking the assistance of Agnes Sampson for pain relief during her labour and the delivery of her two sons. Those attempting to relieve the pain of childbirth by administering drugs were considered guilty of heresy punishable by death.

The modern era of obstetric analgesia began when James Y. Simpson, an obstetrician in Edinburgh, used ether for obstetrics in 1847. A dispute still continues whether Crawford Long of Jefferson, Georgia, U.S.A., first used ether in obstetrics before Simpson. However, Long did not report his use until years later, after Simpson's claim was well established.

The Scottish Calvinist clergy and many prominent physicians including Meigs and Rainsbotham objected to Simpson's use of chloroform to abolish the pain of childbirth. They quoted the previously mentioned excerpt from Scripture and contended that the pain of parturition should be borne with patience and fortitude. Simpson answered that "God was the first anaesthetist", based on the biblical description of how the Creator caused a deep sleep to come over Adam so that a rib could be removed and Eve created (*Genesis*, Chapter II, verse 21).

Respectability was bestowed on obstetric analgesia when Queen Victoria accepted chloroform given intermittently to produce analgesia during the birth of Prince Leopold. The Queen was attended by Sir James Clark and John Snow, the first full-time physician anaesthetist, served as "analgesist".

In the United States, Walter B. Channing, Professor of Midwifery and Medical Jurisprudence at Harvard Medical School, published *A Treatise on Etherization in Childbirth: Illustrated by 581 Cases* in 1848. In his introduction, Channing stated: "My object was to learn if this use of it [ether] has been safe—safe both to mother and to child, and, thus to contribute something towards settling the most important point concerning its future use, namely, that of its safety." In reality, Channing was describing the role of the obstetric anaesthetist—to relieve the pain of childbirth without harming the mother or the fetus—soon to be the newborn.

In the following 130 years, every possible drug or drug combination that was available for use to relieve the pain of childbirth has been evaluated in obstetrics. All these drugs cross the placenta in variable amounts. Difficulties develop when one tries to determine the "safety" of drugs administered to the mother during labour and delivery and to interpret the changes in the newborn which result. Until recently, there was little information on how to evaluate a newborn child, with the exception of the Apgar score.

The Apgar score has been the traditional and the most frequently used criterion for assessing the well-being of the newborn and the effects of obstetric medication. Devised by Dr Virginia Apgar in 1953 to focus attention on the newborn, this scoring system

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has proven to be rapid and reproducible (Apgar, 1953). It is an excellent screening test for vital functions during the first minutes of life; however, the subtle effects of drugs are likely to be overlooked. The five functions (heart rate, respiration, skin colour, muscle tone and irritability) are essentially vital signs. As a predictor of normal neurological development, the Apgar score is a crude tool. Drage and colleagues (1966) found that full-term newborns with Apgar scores of 0–3 had a greater frequency of neurological abnormality at 1 year of life when compared with similar newborns with Apgar scores of 7 or more. However, only 4.2% of full-term newborns with 5-min Apgar scores less than 4 were abnormal at 1 year of age.

Historically, there is no basis for using Apgar scores to study the effects of drugs in the newborn. All the mothers of the neonates examined in Apgar's original report had received some kind of pain relief. Many drugs used in obstetrics that were thought to have no effect on the newborn when evaluated by the Apgar score have been found to have discrete influences when neurobehavioural testing is performed.

DEVELOPMENT OF NEUROBEHAVIOURAL ASSESSMENT TECHNIQUES

Neurobehavioural assessment is not a standard part of the newborn examination, which includes: the Apgar scoring of physiological functioning at birth; monitoring vital signs (heart rate, respiration, temperature and, in an increasing number of institutions, arterial pressure); the Dubowitz scale for assessing gestational age and a screening evaluation of the presence or absence of specific reflex responses of the newborn.

Graham and colleagues (1957) developed one of the earliest neonatal behavioural assessments that included an evaluation of motor strength, sensory responses to visual and auditory stimuli, tactile adaptive responses, pain thresholds and irritability. The characteristic response of the infant was scored, whereas, in the Rosenblith modification of Graham's scale, the best performance was noted and the pain threshold test was eliminated.

Subsequently, Prechtl and Beintema (1964) developed an in-depth test of neonatal responses which evaluated the presence or absence of a series of reflexes including the sleep or awake state, posture movement, general activity, tremor, skin colour, breathing and twitching. This extensive test is still primarily neurological and not behavioural in its character.

Desmond and her colleagues (1963) described a characteristic series of changes in the vital signs and behaviour of healthy infants during the first 6 h of life. There is an initial period of reactivity occurring immediately after birth, followed by an unresponsive interval, which, in turn, is followed by a second period of reactivity.

The initial period of reactivity includes tachycardia, rapid and irregular breathing, a decrease in body temperature and increased body tone and exploratory behaviour. Following this initial period of alertness, an unresponsive period occurs between 1 and 4 h of age after the newborn has left the delivery room and is characterized by a decrease in activity, heart rate and breathing, and the infant sleeps. Upon awakening, the infant becomes responsive to its environment. Desmond concluded that the effects of drugs given during labour and delivery may not be apparent during the first period of reactivity because of the stimulation of the delivery process, but would become evident during the unresponsive interval. Thus, infants whose mothers had received analgesia or anaesthesia are more accurately described as "recovering patients". Recovery from drug effects begins after delivery when placental circulation to the fetus—now newborn—ceases and the infant begins to eliminate the drug(s) directly or as metabolites. A good beginning—a good Apgar score—does not rule out the possibility of problems arising during the first few hours of life.

In the 1960's, Brazelton of the Boston Children's Hospital Medical Center developed a neurobehavioural examination which, while based on Prechtl and Beintema's "Neurological Examination of the Full Term Infant", is primarily an attempt to score the infant's responses to his environment (Brazelton, 1973).

It is important to remember that testing newborn behaviour has some basic problems which include observer bias, difficulty in making measurements, control of the environment and potential bias in population selection. One must consider gestational age, obstetric history and variability of response in the normal newborn. Response decrement behaviour (habituation) requires an intact central nervous system capable of integrating stimuli and is of important prognostic value. States of consciousness (wake–sleep cycles) influence response and are factors in behavioural and neurological function.

The baby's state of consciousness is probably the most important element in the Brazelton "Neonatal Behavioural Assessment Scale". The newborn's responses to all stimuli are dependent upon his state of consciousness. This examination specifically evaluates the state before each item of the examination; thus, its variability becomes an important dimension.

Response decrements (habituation) to light, rattle, bell, pinprick, orientation to auditory and visual stimuli, alertness, general tonus, motor maturity, pull-to-sit, cuddliness, defensive movements, consolability, excitement, rapidity of response (build-up), irritability, activity, tremulousness, startle, lability of skin colour and states, self-quieting activity, hand-to-mouth facility and smiling are the items observed and recorded. Reliability of independent testers range from 0.85 to 1.00. If this examination is used for research, it is advisable to use two trained testers for comparison.

Although Brazelton designed his assessment for the normal newborn infant, its use in comparing infants within and across cultures has been demonstrated. Its potential for evaluating the abnormal newborn gives the examination a broad spectrum of applicability.

In 1974, in an attempt to study the effects on the newborn of extradural anaesthesia administered to the mother during labour and delivery, Scanlon and his associates (1974) at the Boston Hospital for Women devised a neurobehavioural examination that utilized elements adapted from Prechtl and Beintema's neurological examination of full-term newborn infants and Brazelton's Neonatal Behavioural Assessment Scale. The test is clinically applicable, easy to perform, rapid and inexpensive. Personnel can be trained in 2 or 3 days to 85% reliability while it takes 3–4 weeks to train adequately an examiner to the same level of reliability with the more comprehensive Brazelton examination.

The proforma for the Scanlon neurobehavioural assessment (table I) includes an evaluation of the newborn's state of consciousness before each individual observation. Response decrement behaviour (habituation) to pinprick, resistance against passive motion (pull to sitting, arm recoil, truncal tone and general body tone), rooting, sucking, Moro response, habituation to light and sound, placing, alertness and general assessment are graded on a numerical scale (0–3). Finally, a judgement is made on the lability of state exhibited by the newborn during the examination. The examiner should be unaware of the anaesthetic management of the mother and not be involved in the care of the infant.

RESULTS

Brazelton (1970), in 1961, found that the maternal administration of quinalbarbitone 150 mg and

TABLE I. *Proforma for neurobehavioural assessment*

Name________________ Unit Number________

Time____________ Blood-Gases Po_2____ Pco_2____ pH____

Anaesthetic Level________ Type________ Body Temp.________

Apgar HR____ Resp. Eff.____ Tone____ Irrit.____ Colour____ Total____

NEURO EXAM.:

STATE ____ 1. Response to pin prick 0 1 2 3
Habituation no.____
____ 2. Resistance against passive motion
A. Pull to sitting 0 1 2 3
B. Arm recoil 0 1 2 3
C. Truncal tone 0 1 2 3
D. General body tone 0 1 2 3
____ 3. Rooting 0 1 2 3
____ 4. Sucking 0 1 2 3
____ 5. Moro response 0 1 2 3
Threshold (no. of attempts)____
Extinguishment____
____ 6. Habituation to light in eyes no.____
____ 7. Response to sound 0 1 2 3
Habituation no.____
____ 8. Placing 0 1 2 3
9. Alertness 0 1 2 3
10. General assessment A B N S
(circle)
Reasons
State____________________
Lability of State ____________________

COMMENTS:

scopolamine 0.4 mg less than 6 h before delivery resulted in 24–48 h of lag in the ability of the newborn to adapt to breast feeding. Mothers in this group reported that their babies were less alert, more difficult to arouse and had more problems with suckling.

Kron, Stein and Goodard (1966) demonstrated that the newborn of mothers who had received 200 mg of quinalbarbitone during labour demonstrated poorer sucking responses and lower formula intake during the first 4 days after delivery than newborn whose mothers had not been so sedated.

Borgstedt and Rosen (1968) described neonatal behavioural changes consisting of alterations in waking, arousal and muscle tone with the administration of sedatives, hypnotics and narcotics to the mother. These changes and altered e.e.g. patterns persisted for 3 days and could not be correlated with the Apgar scores at delivery.

Stechler (1964) found a correlation with drugs given to the mother and decreased visual attentiveness in the newborn between the 2nd and 4th day of life. The quantity of narcotic, tranquillizer or barbiturate administered to the patient before delivery was related directly to shortened visual scanning and observation times in the baby.

Conway and Brackbill (1970) used four different behavioural and psychological tests on 20 infants for 4 weeks after birth with evaluations at regular intervals. They observed that analgesia and anaesthesia administered to the mother had definite effects on sensorimotor function in newborns demonstrated by impaired muscular, visual and neurological performance. The greatest effect was seen with general anaesthesia, but a lesser effect was present after regional anaesthesia. The importance of this work is that persistent and reproducible behavioural effects were demonstrated after both general and regional anaesthesia.

More recently, Brackbill and others (1974) have evaluated infants born to mothers who had received extradural analgesia and either no drug or doses of 50–150 mg of pethidine during labour. Infants of mothers who had not received pethidine habituated to sound twice as fast as did infants of mothers who had received pethidine. Again, there was a direct correlation between dose and response.

However, there are limitations to neurobehavioural studies. A serious problem exists when there are basic inadequacies in patient selection or limitations of the investigator's knowledge of obstetric anaesthesia and perinatal pharmacology. A classic example of this difficulty is demonstrated by the study of Stanley and colleagues (1974) who attempted to correlate regional anaesthesia and newborn neurobehaviour utilizing the Brazelton scale on the 3rd day after birth. Unfortunately, the narcotics (pethidine and morphine) and the tranquillizers (promethazine and hydroxyzine) were all considered together as analgesics. Pudendal, paracervical, extradural and subarachnoid blocks were all listed as "anaesthesia". Comparisons were made between "no analgesia" and "no anaesthesia" and various combinations of each. Thus, the clustering of the subject groups, the grouping together of techniques without regard to the drugs or doses used, the failure to define selection criteria for admission to the study (gestational age or mode of delivery) and the single administration of the assessment at a late date to evaluate the effects of medication, negate the validity of their findings and any apparent correlations.

Scanlon and colleagues (1974) utilizing the Scanlon neurobehavioural examination, described previously, evaluated babies whose mothers had received extradural anaesthesia with mepivacaine or lignocaine and compared them with babies whose mothers received low spinal, local or no anaesthesia. The extradural group contained a higher proportion of infants who failed to habituate to certain forms of stimulation, such as pinprick and the Moro manœuvre. In tests assessing muscle strength and tone, the extradural anaesthesia group scored lower than the non-extradural group. In general, the extradural babies could be characterized as "floppy but alert". Subsequently Tronick and colleagues (1976), using the Brazelton examination, found that all evidence of diminished muscle tone disappeared within the first 12 h of life.

Scanlon and others (1976) evaluated a similar study group of newborns whose mothers received bupivacaine for extradural anaesthesia. These babies were comparable with the non-extradural group. In fact, in some of the tests, the bupivacaine group appeared to score better than the control group although the differences were not statistically significant. These differences may be a result of the smaller dose of bupivacaine, the longer time from last injection to delivery, high maternal plasma protein binding and subsequent decreased placental transfer.

Hodgkinson and colleagues (1977) recently evaluated newborns whose mothers received lumbar extradural anaesthesia with 2-chloroprocaine, thiopentone–nitrous oxide and ketamine–nitrous oxide for vaginal delivery. Lumbar extradural anaesthesia with 2-chloroprocaine was associated with the greatest percentage of high scores on both the first and second day for overall assessment, tone, rooting, sucking, Moro's response, placing, alertness and habituation to pinprick. The scores were lowest after thiopentone and intermediate following ketamine. No relationship could be found between neurobehavioural responses and the use of outlet forceps, oxytocin stimulation, parity or duration of labour. However, no control group was available for comparison and the Scanlon examination was first administered between 4 and 24 h of life. It is my opinion that the assessment should be carried out between 2 and 4 h of age to coincide with the unresponsive period observed by Desmond when the effects of drugs administered to the mother are most likely to be present. Also, one of the difficulties in evaluating ketamine by neurobehavioural technique is that the drug produces its effect by excitation of the central nervous system. It is conceivable that sufficient ketamine crosses the placenta to stimulate the brain and, subsequently, produce an increase in activity in the newborn, thereby giving inaccurate high scores during the assessment.

Corke (1977) compared three groups of neonates—no analgesia *v.* pethidine and promazine *v.* bupivacaine extradural—utilizing the Scanlon examination within 4 h of delivery and found that infants born to mothers who had received pethidine and promazine scored significantly less than babies of mothers who received no analgesia or lumbar extradural anaesthesia with bupivacaine. The extradural group scored better than the "no analgesia" group in all tests except muscle tone. However, the differences were not statistically significant.

In a preliminary communication, McGuinness and others (1978) found that when bupivacaine extradural block was employed for Caesarean section there were no discernible neurobehavioural effects.

Lund and others (1977) evaluated etidocaine for Caesarean section and found no neurobehavioural changes in 40 infants assessed within 2–4 h of delivery.

Palahniuk and his associates (1977) compared three anaesthetic techniques in an attempt to make a choice for Caesarean section: (1) thiopentone induction with 70% nitrous oxide in oxygen maintenance, (2) thiopentone induction with methoxyflurane 0.2–0.5% in oxygen maintenance and (3) extradural anaesthesia (carbonated lignocaine 1.73% with 1 : 200 000 adrenaline) with oxygen supplementation. Neurobehavioural assessment of the newborn was performed at 6 and 24 h of age by a neonatalogist who had no knowledge of the type of anaesthesia administered to the mother. There was decreased muscle tone, alertness and general assessment in the nitrous oxide in oxygen group and poor muscle tone in the extradural group. Tone was significantly better in the methoxyflurane group at 6 h and general improvement in scores came about between 6 and 24 h in each group. Although there was no obvious superiority of any particular technique in this study, the nitrous oxide group fared worst while the extradural group was similar to the methoxyflurane group, with the exception of decreased muscle tone.

Corke, Datta and Ostheimer (1978), in a preliminary communication, evaluated the neurobehaviour of infants born to mothers with and without hypotension (systolic arterial pressure less than 90 mm Hg) following spinal anaesthesia. The occurrence of hypotension in the mother was reflected by acidosis in the infant at delivery even when the hypotension was corrected within 2–3 min. When the babies were examined between 2 and 4 h of age, no neurobehavioural differences were found in either group. We postulated that, if the hypotension was allowed to continue for a longer period of time, there might be evidence found of changes in central nervous system function.

Hollmén and colleagues (1978) evaluated the effect of extradural anaesthesia with 1.5% lignocaine and 1 : 200 000 adrenaline and general anaesthesia using thiopentone, nitrous oxide in oxygen and suxamethonium infusion on the neurological activity of newborns following Caesarean section. There was a significant correlation between maternal hypotension (mean arterial pressure less than 70 mm Hg) and weak rooting and sucking reflexes in newborn whose mothers had received lumbar extradural anaesthesia. The maximum duration of hypotension was 10 min in one patient, the average time being 5–6 min. Infants of high-risk obstetric patients had abnormal neurological activity regardless of the anaesthetic technique employed. Thus, this work extends the work of Corke and colleagues and confirms the hypothesis that maternal hypotension if not corrected will cause alterations in the infant's neurobehavioural status. Perhaps these changes in the newborn would be apparent more readily if ephedrine was not used to correct the hypotension, since it readily passes the placenta and may cause shivering in the newborn.

In conclusion, neurobehavioural assessment is becoming a tool in the armamentarium of the perinatal team for use in evaluating the effects of maternally administered drugs on the newborn. Continued evaluation of the various classifications of the "normal" neonate will eventually delineate what is normal. Initial studies in measuring the effects of drugs on the abnormal or "at risk" newborn have begun and these works will further enhance our ability to manage the "at risk" parturient and her newborn. The perinatal period is the only time that two lives are in jeopardy simultaneously.

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EFFECT OF OBSTETRIC REGIONAL ANALGESIA ON THE CHANGE IN RESPIRATORY FREQUENCY IN THE NEWBORN

L.-E. BRATTEBY, L. ANDERSSON AND S. SWANSTRÖM

The effects of different forms of obstetric anaesthesia and analgesia on the infant have been investigated extensively during the past 15 years. In most studies assessment of the condition of the newborn has been based upon the Apgar score, blood chemistry and acid–base status. It is now clear, however, that some significant effects on neonatal adaptation are not necessarily reflected by these tests. Changes in the e.e.g. (Borgstedt and Rosen, 1968), neonatal sucking behaviour (Kron, Stein and Goddard, 1966) and neonatal neurobehaviour (Scanlon et al., 1974; Tronick et al., 1976) have been demonstrated in infants with normal Apgar score, blood chemistry and acid–base balance.

As part of an investigation of regional analgesia with lignocaine, the breathing of the newborn was studied during the first 2 h of life. Some differences in respiratory frequency were found between infants whose mothers received regional analgesia and a control group.

PATIENTS AND METHODS

Patients

Forty-nine full-term infants of length and birth weight appropriate for the gestational age and with a 1-min Apgar score of 8 to 10 were studied. The mothers were healthy and had normal pregnancies and normal vaginal delivery. The parents of all 49 infants were informed about the nature of the study and gave their consent.

Reference group

Fourteen of the 49 infants, whose mothers received 50% nitrous oxide in oxygen during the uterine contractions, formed a reference group.

Regional analgesia groups

The mothers of 24 infants received lumbar extradural analgesia, eight of them by a continuous drip infusion of 0.4% lignocaine, and 16 by intermittent injection of 0.5% lignocaine with adrenaline. Eleven received a paracervical block followed by a pudendal nerve block, with lignocaine and adrenaline. The total amount of lignocaine given to the individual mother in the different groups ranged from 50 to 800 mg. The maximum plasma lignocaine concentration in the infants was between 0.06 and 0.80 $\mu g\ ml^{-1}$ (table I).

TABLE I. *Mean and range of maximum arterial lignocaine concentration of the newborn infants of primiparous and multiparous mothers in the three regional analgesia groups*

Regional analgesia group	Parity of mother	Lignocaine concn ($\mu g\ ml^{-1}$)	
Continuous extradural	Primiparous	Mean	0.43
		Range	0.10–0.68
	Multiparous	Mean	0.29
		Range	0.20–0.50
Intermittent extradural	Primiparous	Mean	0.29
		Range	0.10–0.60
	Multiparous	Mean	0.29
		Range	0.20–0.40
Paracervical block	Primiparous	Mean	0.38
		Range	0.10–0.80
	Multiparous	Mean	0.23
		Range	0.06–0.60

Clinical procedure

After birth the infants were dried carefully and placed in an incubator in the supine position. The ambient temperature in the incubator was adjusted to give the infant an abdominal skin temperature of 36 °C. There were no significant differences in the skin or rectal temperatures between the infants of different groups. Breathing was monitored continuously using a transthoracic impedence pneumograph (Saab Respimeter). The signal from this instrument was transmitted to an ink and FM tape recorder.

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Blood for gas analysis and determination of the lignocaine concentration was sampled from a catheter in an umbilical artery at six intervals during the first 2 h of life, starting at 10 min. For measurement of arterial pH, Po_2 and Pco_2 an Instrumentation Laboratories pH-blood-gas analyser 313 was used.

The lignocaine concentration was determined by gas-chromatography.

Estimation of respiratory frequency

The analog transthoracic signal recorded on FM tape was digitized, using a Siemens 305 computer. The subsequent signal analysis was performed by an IBM 370/155 computer. The influence of undesirable factors on the transthoracic impedance signal, such as base-line variations from body movements, cardiac activity and high-frequency noise, was reduced. A

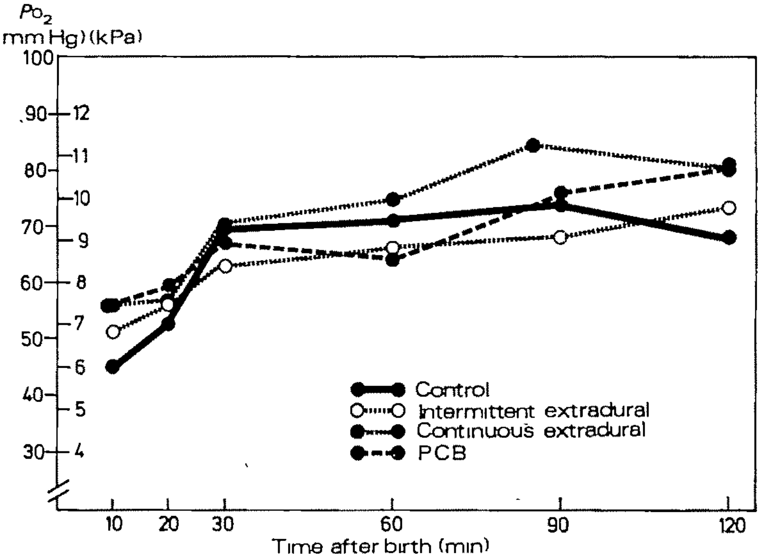

FIG. 1. Mean values of arterial Po_2 in newborn infants of the control and regional analgesia groups.

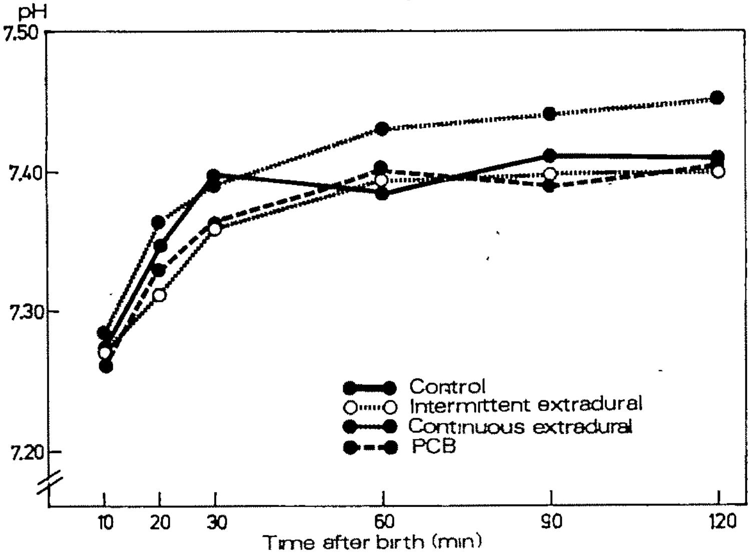

FIG. 2. Mean values of pH in newborn infants of the control and regional analgesia groups.

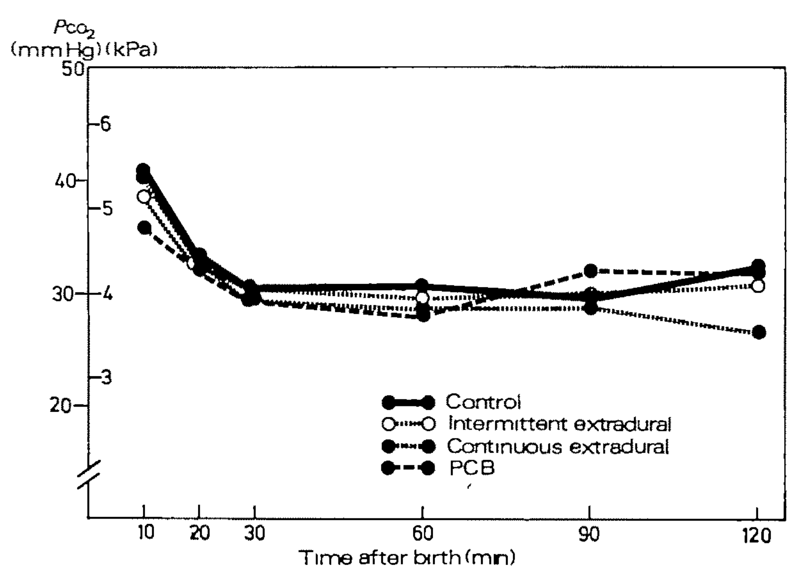

FIG. 3. Mean values of arterial $P\text{CO}_2$ in newborn infants of the control and regional analgesia groups.

breath was defined as a cyclic variation of the preprocessed transthoracic impedance signal (Andersson and Bratteby, 1978). The mean respiratory frequency for each successive 15-min period was calculated during the first 2 h of life.

RESULTS

There were no significant differences in arterial $P\text{O}_2$, $P\text{CO}_2$ or pH between the different groups during the first 2 h of life (figs 1–3). The mean respiratory frequencies for successive 15-min periods in the reference group are in figure 4. Early after birth this frequency was high, but during the first 2 h it showed a marked and steady decrease. No significant difference in the respiratory frequency during the first 2 h of life was found between infants of primiparous and multiparous women of the reference group. The two extradural groups did not differ significantly from each other in their respiratory rates and the results were combined. The mean respiratory frequencies in infants of multiparous women of the extradural and paracervical groups did not differ significantly from those in the infants of the reference group. In infants of primiparous women, however (fig. 5), the mean respiratory frequencies in the extradural (74.5 ± SD 8.5 b.p.m.) and the paracervical (75.9 ± SD 9.5) groups were initially significantly less ($P < 0.005$ and $P < 0.05$ respectively) than the rate in the reference group (83.9 ± SD 5.3). In the infants of the extradural group of primiparous mothers there was no significant change in mean respiratory frequency during the first 2 h of life, in contrast to the reference group. The change in mean respiratory frequency of the infants of the corresponding paracervical group did not differ significantly from that in the reference group.

In the reference group the decrease in respiratory frequency during the first 2 h of life was significantly related to the duration of the second stage of labour (fig. 6). No correlation between duration of labour and change in respiratory frequency was found in any of the regional analgesia groups (fig. 7).

DISCUSSION

The respiratory frequency in individual newborn infants varies considerably partly in relation to the state of sleep (Prechtl and Leonard, 1967) and activity. However, the mean respiratory frequency and its relation to labour in a group of newborn infants whose mothers were not given regional analgesia show some characteristic features which are identical in infants of primiparous and multiparous women (cf. figs 4 and 6). In the present study the results for the newborn infants of the regional analgesia groups were in some respects significantly different from those of the reference group, but were also more complex. Thus, in the extradural group the change in mean respiratory frequency differed between newborn infants of primiparous and multiparous mothers. The discrepant postnatal respiratory frequency patterns in the

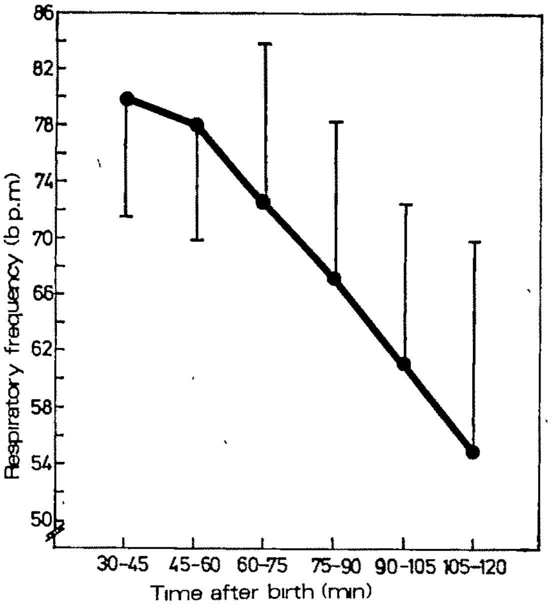

FIG. 4. The mean respiratory frequency ±1 SD of successive 15-min periods in newborn infants of the control group.

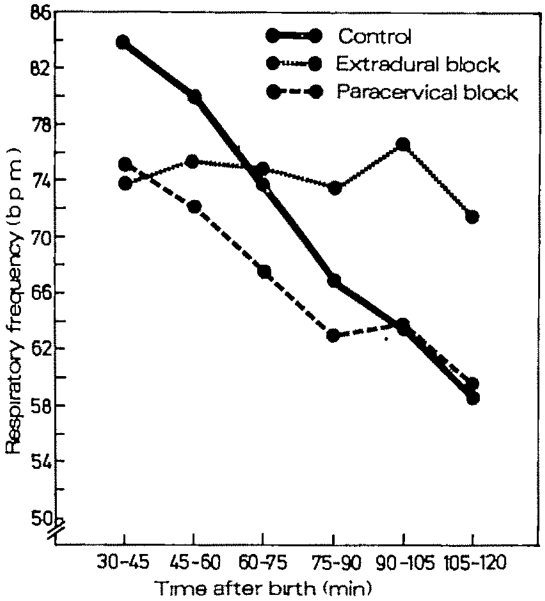

FIG. 5. The mean respiratory frequency of successive 15-min periods in newborn infants of primiparous women in the control and regional analgesia groups.

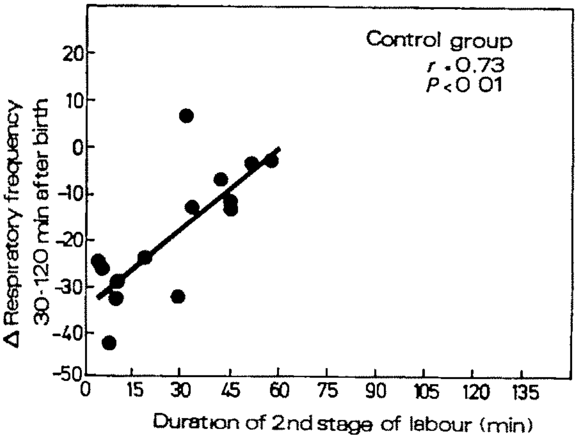

FIG. 6. Correlation between duration of second stage of labour and change in respiratory frequency early after birth in the control group.

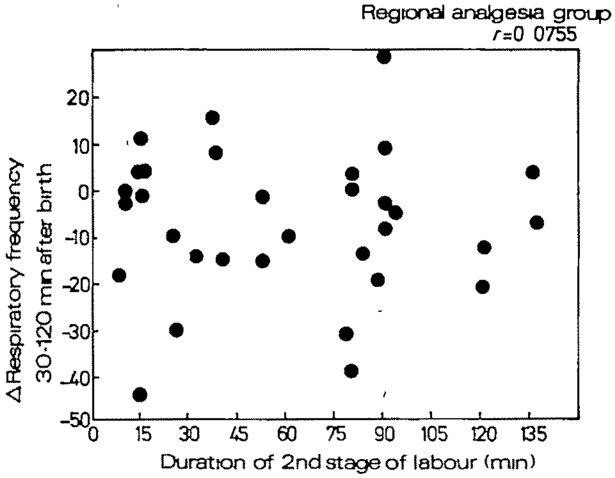

FIG. 7. Relationship between duration of second stage of labour and change in respiratory frequency early after birth in the regional analgesia groups.

different groups contrasted markedly with the similarity of postnatal blood-gas and pH values in the same groups. The same blood-gas status was thus achieved by different frequencies and patterns of change of the respiratory frequency in the different groups.

The differences in mean respiratory frequencies between infants of the reference group and those of the regional analgesia group are probably not a result of a pure pharmacological effect of lignocaine, as no significant correlation was found between the serum concentration of lignocaine in the infants and the respiratory frequency or its changes. The results may indicate that the different respiratory frequency patterns are a result of combined effects of factors involved in the methods of regional analgesia on the course of labour and on the fetus and newborn infant. The differences in mean respiratory frequency between the infants of mothers who did and did not receive analgesia represent discrete but objectively measurable signs which, to the best of our knowledge, have not been described before. It is not possible on the basis of the present study to discuss the results in terms of positive or negative effects of regional analgesia on the newborn. The findings have to be confirmed by other workers and the pathophysiological background of the observations has to be more extensively investigated before any further conclusions can be drawn.

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Our sincere thanks are due to Dr Bo A. Nilsson, Department of Obstetrics and Gynecology, and to Dr Gunilla Willdeck-Lund, Department of Anaesthesiology, University Hospital, Uppsala, for valuable contribution to this study. The study was supported by grants from the Bank of Sweden Tercentenary Foundation.

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DISCUSSION

DR FINSTER: Would Dr Ostheimer give us his views on the long term importance of neurobehavioural disorders in the neonatal period.

DR G. OSTHEIMER (BOSTON): I really have no idea what the long term importance will be. Dr Brazelton and his group have initiated a study of babies who received both the Scanlon and Brazelton examinations at birth and who will be followed for 7 years. The children will be studied to determine their neurological development, their school progress and their social interactions. The Brazelton people are convinced that their superior babies, that is those whose mothers receive either no analgesia or extradural block with bupivacaine, have much better social interaction with their parents and will turn out to be superior children later on. However, I am not prepared to give an answer or even speculate until I have seen the results of our own and these studies in the years to come.

DR L.-E. BRATTEBY (UPPSALA): In our follow-up of children 18 months after birth we have been unable to demonstrate a difference between the control group and the groups receiving regional analgesia.

DR ROSEN: Although it seems unlikely to me that these tests will predict future abnormalities in otherwise normal children, we are duty bound to carry out the measurements until their importance has been properly established. One of the problems is that most of the reported studies have not stated the doses of drugs being given, or measured the plasma concentrations that were reached. Hence we have no data on dose–response.

Could I ask Dr Bratteby if blood-gas analyses performed in the neonates were measured from heel-stab samples because this may have the effect of stimulating the children to hyperventilate?

DR BRATTEBY: All the blood samples were obtained from an umbilical artery catheter.

DR BONICA: The dosage of drugs used in extradural blocks varies greatly from centre to centre and, if it is the local anaesthetic which is causing the neurobehavioural disorders, then clearly the dose and the plasma concentrations achieved must be of some importance.

DR OSTHEIMER: We do have data on the plasma concentrations of bupivacaine in some of the patients in the current longitudinal study which will proceed for 7 years. Unfortunately, the original group done with lignocaine did not have blood concentrations measured. What is badly needed is a clean control group, that is mothers who received no medication at all during their labour. The only such group I know in the literature was that published by Corke (reference in my paper), and his group consisted of only 14 mothers.

DR H. ALBRECHT (DUSSELDORF): Am I right in thinking that, in the group of babies that you studied, all had a normal pH?

DR OSTHEIMER: Yes; our group consisted of "super normal" babies. The pregnancies had to be normal, the labours had to be normal, the maternal arterial pressures had to be normal and the neonates' umbilical artery pH were 7.25 or greater. When these criteria were not fulfilled, the case was discarded from the series.

DR ALBRECHT: Surely, what we need now is to know the neurobehavioural status of babies who have a pathological pH, which can of course occur with a vaginal delivery even after a totally normal pregnancy?

DR OSTHEIMER: Certainly the next step will be an examination of babies from abnormal pregnancies and labours. However, before we can make comparisons with this group we must have an absolutely normal group for comparison. Workers studying neurobehavioural patterns differ widely in their criteria and in their subjective assessments. We have tried, therefore, to make our tests as objective as possible and to define our criteria strictly.

DR ALBRECHT: Is it not possible that the acidotic baby will have a greater brain concentration of the drug?

DR OSTHEIMER: Yes.

DR FINSTER: The National Institute of Health in the United States sponsored a collaborative study of 50 000 mothers and their children, the latter being followed up for a number of years. This investigation has virtually failed because most of the results have turned out to be useless. It is almost impossible to decide whether any abnormality detected in a child is due to factors occurring during pregnancy, during labour or following birth. Is the Brazelton study liable to avoid the same pitfalls?

DR OSTHEIMER: Of course there are serious difficulties in performing this kind of study. In Brazelton's study he is only following a small number of "normal" children and therefore his results will only be relevant to that group.

DR J. THORBURN (GLASGOW): Would Dr Ostheimer tell us how gestational age was determined in his group?

DR OSTHEIMER: The assessment was done by the obstetrician concerned and taken straight from the medical records.

DR THORBURN: There could be some variability, therefore, in the gestational age of the children?

DR OSTHEIMER: The gestational age varied from 37 to 41 weeks in the bupivacaine study and from 38 to 42 weeks in the other studies.

DR T. E. GORDH (UPPSALA): May I ask if there was any contact between the neonate and its mother during the first hour of life? This is now considered to be a very important factor in mother/baby relationships.

DR OSTHEIMER: In our bupivacaine group the baby was with the mother and father for the first 1–1½ h of life. It was then removed to the nursery, had its physical examination, was made confortable and had its neurobehaviour assessed 3–4 h after birth. The examination lasts approximately 10–15 min.

DR BONICA: Is there any evidence, as opposed to opinion, that mother/baby contact in the first hour of life is important to the child's development?

DR OSTHEIMER: No, there is no evidence for it. We are all tending to over-react to consumerism. One group which claimed that it was of great importance 10 years ago are now saying that perhaps it is not so important after all.

DR ROSEN: There has been one study published from Oxford (Whiten, 1977) which showed that babies admitted to special care units for 2–14 days or longer did show disorders for 2 months following this, but no difference could be detected by 3–4 months. If seriously ill babies cannot be shown to be permanently damaged, then it seems unlikely that otherwise well babies will be affected.

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COMPARATIVE STUDY OF VARIOUS LOCAL ANAESTHETIC SOLUTIONS IN EXTRADURAL BLOCK IN LABOUR

D. G. LITTLEWOOD, P. BUCKLEY, B. G. COVINO, D. B. SCOTT AND J. WILSON

In assessing the effects of local anaesthetic drugs it is highly desirable to use a double-blind technique. In a previous study (Littlewood et al., 1977), we reported some of the effects of plain solutions of bupivacaine, lignocaine and etidocaine as used for extradural block in labour. That study indicated that the strength of solution was important in determining the onset and duration of sensory analgesia and degree of motor blockade of these agents. As adrenaline is commonly added to local anaesthetic solutions to reduce absorption and to intensify and prolong their analgesic effect, the following study was designed to compare plain solutions and those containing adrenaline in a double-blind fashion. A solution of 0.125% bupivacaine was included in this study as it has been reported to be efficacious in relieving the pain of labour (Vanderick et al., 1974).

METHOD

Eighty patients aged 18–44 yr were studied. Each was about to receive extradural anaesthesia for labour and was allocated to one of eight groups in the trial. There was no significant difference in mean age, height or weight between the groups. An indwelling extradural catheter was inserted via the L2/3 or L3/4 interspinous space and a test dose of 2% lignocaine 3 ml was given through it. Once the onset of labour was established, as defined by the presence of regular and painful contractions and not sooner than 20 min after the test injection, 10 ml of the appropriate agent was injected in a randomized double-blind manner. A 10-ml volume was used as this was considered adequate to ensure that any failure of analgesia was attributable to the drug or its concentration and not to inadequate spread of solution.

The solutions tested were 2% lignocaine, plain and containing 1 : 200 000 adrenaline, and bupivacaine 0.125%, 0.25% and 0.5%, plain and with 1 : 200 000 adrenaline. If a solution containing this concentration of adrenaline was not commercially available, the vasoconstrictor was added, in the appropriate quantity from a freshly opened ampoule, to a plain local anaesthetic solution.

The following observations were made after injection of the solutions:

Efficacy. Twenty minutes after injection this was graded on a 1–4 scale as 4 = good relief (no pain), 3 = moderate relief, 2 = slight relief and 1 = little or no relief.

Onset time. The time (min) from injection to the first contraction described by the patient as "not painful".

Duration. The time (min) from injection to recurrence of painful contractions.

Dermatomal spread. The extent of analgesia to pinprick 20 min after injection.

Motor block of the lower limbs. Twenty minutes after injection this was graded on a 1–4 scale: 1 = able to bend knees against resistance, 2 = able to bend knees against gravity, 3 = able to bend knees with some assistance and 4 = no significant voluntary movement.

Mean arterial pressure. Measured before injection and at 5-min intervals thereafter by sphygmomanometry with the patient in a lateral position and the cuff on the superior arm.

Although there were 10 patients in each group, where an injection was classed as giving no relief or only slight relief it was obviously impossible to measure either onset time or duration of analgesia by the above criteria. The remaining patients in such a group thus represent a selected population.

Statistical analysis was carried out using Student's t test where appropriate and χ^2 test for grouped data.

RESULTS

Efficacy. The frequency of adequate analgesia produced by each test solution of bupivacaine improved as the concentration was increased and with the addition of adrenaline (table I). In the group of patients receiving the plain solution of 0.125%

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TABLE I. *The analgesic effects of the various local anaesthetic solutions are classified in four groups: good, moderate, slight and none. Also shown are the number in each group where analgesia was considered less than good and the total number of observations in each group*

Drug	Analgesia				Less than good	Number of observations
	Good	Mod	Slight	None		
Lignocaine						
2% plain	9	1	0	0	1	10
2% with adrenaline	10	0	0	0	0	10
Bupivacaine						
0.125% plain	3	4	1	2	7	10
0.125% with adrenaline	5	3	0	2	5	10
Bupivacaine						
0.25% plain	6	2	0	2	4	10
0.25% with adrenaline	10	0	0	0	0	10
Bupivacaine						
0.5% plain	9	1	0	0	1	10
0.5% with adrenaline	9	0	1	0	1	10

bupivacaine, analgesia was considered adequate in only three out of 10, while the addition of adrenaline to this concentration increased the frequency of adequate analgesia to 50%. Four out of 10 patients did not achieve satisfactory analgesia when receiving the 0.25% plain bupivacaine solution, but addition of adrenaline resulted in adequate analgesia in all of the patients. Satisfactory relief of pain was obtained for 90–100% of patients receiving 2% lignocaine or 0.5% bupivacaine with or without adrenaline.

Onset of analgesia. A significant reduction in onset time from 8.7 ± 0.87 min to 5.4 ± 0.63 min occurred when adrenaline was added to 2% lignocaine ($P < 0.005$). This effect was not seen with bupivacaine. In addition, 2% lignocaine with adrenaline had a significantly faster onset than any other solution tested (table II).

TABLE II. *Time from injection to first painless contraction ± SEM (min) for the eight solutions studied during extradural block in labour. The reduced number of observations with the dilute bupivacaine solutions is a result of a lack of discernible onset time where the injected dose gave little or no pain relief*

Drug	Onset time	Number of observations
Lignocaine		
2% plain	8.7 ± 0.87	10
2% with adrenaline	5.4 ± 0.63	10
Bupivacaine		
0.125% plain	9.7 ± 1.88	7
0.125% with adrenaline	11.4 ± 2.83	8
Bupivacaine		
0.25% plain	8.6 ± 1.63	8
0.25% with adrenaline	8.8 ± 1.34	10
Bupivacaine		
0.5% plain	10.6 ± 1.14	10
0.5% with adrenaline	8.8 ± 0.89	10

There was a more rapid onset with increasing concentration of bupivacaine, although this was not statistically significant. It should be remembered that, because of the failure of analgesia with the dilute solutions, the mean values in the 0.125% and 0.25% bupivacaine groups may have been decreased artifically.

TABLE III. *Time from extradural injection to return of painful contractions ± SEM (min) and the number of observations. The same bias is seen with the dilute solutions of bupivacaine as occurred in table II*

Drug	Duration	Number of observations
Lignocaine		
2% plain	68.1 ± 8.4	10
2% with adrenaline	108.3 ± 8.4	10
Bupivacaine		
0.125% plain	67.8 ± 9.3	7
0.125% with adrenaline	70.5 ± 7.8	8
Bupivacaine		
0.25% plain	70.0 ± 8.0	8
0.25% with adrenaline	105.5 ± 13.5	10
Bupivacaine		
0.5% plain	95.0 ± 10.2	10
0.5% with adrenaline	110.2 ± 11.7	10

Duration. The marked effect of the addition of adrenaline to 2% lignocaine was again noted (table III), the duration of analgesia being significantly prolonged by 40 min ($P < 0.0005$). In fact, 2% lignocaine with 1 : 200 000 adrenaline showed a longer duration of analgesia than 0.125% bupivacaine plain ($P < 0.005$) and with adrenaline ($P < 0.0025$) and 0.25% bupivacaine plain ($P < 0.005$). There were longer durations of action when adrenaline was added to the bupivacaine solutions, but this reached significance only with the 0.25% concentration.

Both solutions of 0.125% bupivacaine gave shorter periods of analgesia than 2% lignocaine with adrenaline, 0.25% bupivacaine with adrenaline ($P<0.025$), 0.5% bupivacaine plain ($P<0.05$) and 0.5% bupivacaine with adrenaline ($P<0.01$). Increasing the concentration of bupivacaine lengthened the duration of effect such that the analgesic duration of the 0.5% plain solution was significantly longer than either the 0.125% or the 0.25% plain solutions. No difference was observed between the 0.25% and 0.5% solution of bupivacaine when adrenaline was added.

Motor block. The frequency of significant motor block (table IV) was minimal with the dilute solutions of bupivacaine and greatest with both solutions of 2% lignocaine.

TABLE IV. *The number of patients with moderate or severe motor paralysis (classification 3 or 4) in each group and the number of observations*

Drug	No. with severe motor block	Number of observations
Lignocaine		
2% plain	2	10
2% with adrenaline	3	10
Bupivacaine		
0.125% plain	0	10
0.125% with adrenaline	0	10
Bupivacaine		
0.25% plain	0	10
0.25% with adrenaline	1	10
Bupivacaine		
0.5% plain	1	10
0.5% with adrenaline	1	10

TABLE V. *Mean values for dermatomal segmental spread of pinprick analgesia, and the maximum reduction in mean arterial pressure in each group*

Drug	No. blocked segments	Decrease in m.a.p. (mm Hg)	Number of observations
Lignocaine			
2% plain	10.7	13.4	10
2% with adrenaline	12.6	13.3	10
Bupivacaine			
0.125% plain	8.6	4.6	10
0.125% with adrenaline	7.6	6.0	10
Bupivacaine			
0.25% plain	8.3	4.5	10
0.25% with adrenaline	9.7	7.9	10
Bupivacaine			
0.5% plain	10.3	4.4	10
0.5% with adrenaline	10.7	9.2	10

Segmental spread and mean arterial pressure (m.a.p.). There was a greater dermatomal spread with increasing concentration of local anaesthetic agent (table V). There were, however, no statistically significant differences between groups. The maximum decrease in mean arterial pressure approximately paralleled the segmental spread and did not appear to be significantly influenced by the presence or absence of adrenaline.

DISCUSSION

The purpose of extradural analgesia during the early stages of labour is to provide long periods of pain relief with minimal disturbance of the course of labour or the well-being of the mother or fetus. In recent years, bupivacaine has become increasingly popular for extradural analgesia in obstetrics because of its prolonged action, minimal motor blockade and low maternal/fetal plasma concentrations. A variety of concentrations of bupivacaine ranging from 0.125% to 0.75% have been employed for obstetric analgesia with conflicting claims as to effectiveness. For example, it has been suggested that 0.125% bupivacaine can give satisfactory analgesia during extradural block in labour and is associated with smaller plasma concentrations, which is obviously desirable as regards toxicity (Geerinckx et al., 1974). However, other reports (Stainthorpe et al., 1978) state that 12 ml of a plain 0.125% bupivacaine solution was efficacious in only approximately 50% of cases. Therefore, the present double-blind study of bupivacaine was initiated to determine the minimum concentration which would be useful for extradural analgesia in early labour.

Clearly, the criteria by which analgesia is judged will depend upon the degree of analgesia considered clinically acceptable. If the aim of extradural analgesia is to provide a "painless labour" then, in this study, this was achieved in only 30% of patients using 10 ml of plain 0.125% bupivacaine, in 50% when 1 : 200 000 adrenaline was added to that injection and in 60% of cases in which 0.25% plain bupivacaine was used. Even when satisfactory analgesia was achieved with these solutions, onset was rather slow and its duration short, although motor block was minimal or absent. Therefore, the potential advantages of 0.125% bupivacaine in labour in terms of low toxicity and absence of motor blockade must be weighed against the lack of adequate analgesia in many of the patients. The improvement in the quality of analgesia and duration as the concentration of bupivacaine increased is consistent with our previous results (Littlewood et al., 1977) and indicate again that if plain solutions of bupivacaine are used, a concentration of 0.5% is required to provide a prolonged duration of adequate analgesia.

The use of adrenaline in solutions used for extradural block in labour varies from centre to centre. The addition of 1 : 200 000 adrenaline to the 2% lignocaine solution in this study gave a more rapid onset and a longer duration of analgesia, compared with 2% plain lignocaine. In fact, our results suggest that 2% lignocaine with 1 : 200 000 adrenaline is more rapid in onset and as long lasting as 0.5% bupivacaine, but also causes more pronounced motor block. Adrenaline appears to have rather less effect when used with bupivacaine. Previous studies (Reynolds and Taylor, 1971; Buckley et al., 1978) have shown that adrenaline does not affect the plasma concentration of the drug following injection of bupivacaine or etidocaine to the same degree as with lignocaine. This may be related to the much greater lipid solubility of bupivacaine and etidocaine. The effect on placental blood flow and the fetus of large amounts of circulating adrenaline and other sympathomimetic agents has been studied extensively in animals, but the effect of the small quantities (25–50 mg) used with extradural injections in patients in labour is documented less fully. Jouppila and colleagues (1978) suggested that 20 μg by this route had no discernible deleterious effect on placental blood flow. If, indeed, adrenaline 20–50 μg is safe for use in early labour, then 2% lignocaine, 0.25% bupivacaine and 0.5% bupivacaine solutions with adrenaline appear to provide the longest duration of satisfactory analgesia. While lignocaine may be preferable because of a shorter onset time, bupivacaine appears to produce less motor blockade. In addition, differences in potential toxicity may exist between these two agents. There is evidence to suggest that subtle neurobehavioural changes occur in the neonatal period, even when the baby has a high Apgar score at birth, which may be a direct drug effect. These changes have been shown following maternal regional anaesthesia with lignocaine and mepivacaine (Scanlon, Brown and Weiss, 1974), but further studies with bupivacaine have failed to show similar changes (Scanlon, Ostheimer and Lurie, 1976).

It is obviously desirable to employ the smallest dose of any drug which will provide efficacious results. This and our previous study would suggest that 0.5% bupivacaine is preferable in order to provide a prolonged duration of satisfactory analgesia with minimal motor blockade if adrenaline is not deemed appropriate. However, if adrenaline is not of concern, then 0.25% bupivacaine with adrenaline is likely to provide a long duration of adequate analgesia with minimal motor blockade and minimal potential for toxicity.

SUMMARY

In a double-blind study, 0.125%, 0.25%, 0.5% bupivacaine and 2% lignocaine with and without adrenline 1 : 200 000 were compared with regard to efficacy, onset time, duration of analgesia, motor block and dermatomal spread of pinprick analgesia, during extradural block in the early first stage of labour. The frequency and duration of adequate analgesia, degree of motor block and dermatomal spread increased as the concentration of bupivacaine was increased, while the onset of analgesia decreased slightly. Adrenaline enhanced the frequency and duration of analgesia and degree of motor block of all the anaesthetic solutions. The highest frequency and longest duration of adequate analgesia occurred with the 0.25%, 0.5% bupivacaine and 2% lignocaine solutions containing adrenaline, whereas 0.5% bupivacaine provided the longest duration of analgesia of the plain anaesthetic solutions.

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THE TEACHING OF OBSTETRIC EXTRADURAL ANALGESIA*

A Personal View

A. DOUGHTY

The ability successfully and safely to manage an extradural block for the relief of pain in labour does not come as a natural instinct to anaesthetists; it is nevertheless a skill that can be readily and rapidly acquired if the teaching is concentrated and effective.

The practice of continuous extradural analgesia has been slow in spreading in Europe. It is probably better developed in Britain than in any other European country and considerable progress has been made against the background of medical and lay prejudice and the shortage of anaesthetists with suitable experience in our National Health Service. A prerequisite for training is the existence of an obstetric department with a well-developed extradural service, and yet such training facilities vary throughout the country. A recent enquiry of the London Teaching Hospitals has shown that, in 1976, the percentage of all confinements in which extradural analgesia was given varied from 62% in one hospital down to 5% in another (Doughty, 1978). A low extradural rate in any teaching hospital must imply that anaesthetists emerge from their training presumably fully equipped for specialist status according to the regulations laid down by the Faculty of Anaesthetists, but quite untrained to become involved in an extradural service. This situation may well persist until the Faculty prescribes specific training in obstetric analgesia.

On the other hand, the approval in 1970 by the Central Midwives Board of England and Wales for midwives to undertake the topping-up procedure has undoubtedly been the spur to the development of extradural services in many of our hospitals. Thus the medical skill of setting up the extradural block can be segregated from the responsible but lesser skill of maintaining analgesia by giving the supplementary injections through a cannula safely sited in the extradural space. It follows that, while one's teaching of doctors should cover the whole field of extradural analgesia, one must also assume responsibility for the training of midwives in the care of the patients enjoying its benefits. In fact the Central Midwives Board rules include the statement that the full responsibility for the extradural block must still rest with the doctor performing it, that the midwives must be properly instructed in the procedure and that the primary dose through the cannula must be given by the doctor. In 1971 the Board prescribed for midwives in training "participation in advanced analgesic techniques under the supervision of a registered medical practitioner". Thus, at least in England and Wales, the principle has been accepted that midwives enter into a partnership with the doctor in maintaining the continuity of analgesia.

As with any innovation, the practice has advantages and disadvantages. The obvious advantage is that the analgesia can be maintained continuously, leaving the anaesthetist free to pursue other work away from the labour ward. A disadvantage is that the discretion of when to give the top-up is left in the hands of midwives whose experience of the method may be variable and whose enthusiasm for total analgesia may be unpredictable.

We have then to determine: *whom* do we teach? *How* do we teach? *What* do we teach?

Whom do we teach?

I would say that we teach any doctor, be he anaesthetist or obstetrician, who is willing to take the trouble to learn, and we have also to teach midwives to play their part in assisting the doctor and in caring for the patients.

How do we teach?

The main plank of teaching in my own hospital is a locally produced booklet revised every year and issued to all who practise extradural analgesia. It is also issued to all midwives and to pupil midwives to whom a special section is addressed dealing with the

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topping-up procedures and the detailed nursing care of the patients. Special emphasis is given to the avoidance and treatment of the effects of aorto-caval occlusion.

I believe that teaching of doctors is most effective if it is intensive, continuous, individual and extends over a period of 2 weeks under graduated supervision. Further, it is most important that the active practice of the technique should be continued in the parent hospital immediately following the intensive course. The demonstrations and practical work in the labour wards are supplemented by tutorials with film and still projections and by the provision of a compendium of reprints of relevant publications on all aspects of the subject.

What do we teach?

One cannot cover the whole field in a short period of training, but one can at least launch a fairly competent performer into practice by close attention to four fundamental points:

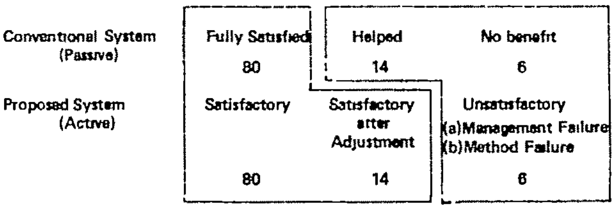
(1) Skill, speed, safety and finesse of technique
(2) Ensuring the reliability of the block
(3) Reduction of side-effects
(4) Avoidance of complications

The early training concentrates on the first two points. The ability to set up an extradural block speedily and skilfully depends not only on effective teaching, but also on establishing a standard routine in the labour ward to be practised by the anaesthetist and by the midwife who is helping him. Standard instructions are placed in each labour ward and these are framed so that any midwife who has never previously seen an extradural block given can give effective help to the anaesthetist without his even speaking a word to her. The standard routine for the doctor is prescribed not only for the preparation and testing of the equipment but also for the orderly, safe and considerate performance of the insertion of the Tuohy needle and extradural cannula. Stress is placed on the initial correct siting and alignment of the needle so that the extradural space is penetrated at the first attempt. Bad technical habits are eliminated before they become established. In particular, the attitude that inadvertent dural puncture is acceptable during training is discouraged by the teaching of a safe technique based on the belief that such an event is an avoidable accident.

Nonetheless, unnecessary delay is not tolerated. There is no reason why the anaesthetist's stock-in-trade of organized efficiency in the anaesthetic room should be abandoned when setting up an extradural block in the labour ward. After all, the relief of severe pain is a matter of some urgency to the sufferer, and a quick, efficiently-given extradural block can be fitted into a busy timetable when a tedious time-consuming ritual cannot.

The second important principle in teaching is to instil a sense of obligation to ensure that, once an extradural block is undertaken, every effort must be made to provide continuous and perfect pain relief for the mother until delivery. In order to maintain high standards of supervision by the midwives it is essential that every patient who has received extradural analgesia should be followed up so that the quality of the analgesia achieved can be assessed, as it is only by identifying the source of unsatisfactory analgesia that improvements can be made in the service.

Unhappily, a somewhat passive attitude towards the management of an extradural block is prevalent and this is epitomized by the conventional classification of the assessment of extradural efficacy by which each is graded as "fully satisfied", "helped" or "no benefit" (Crawford, 1972). Now, as I believe that the category "helped" implies some degree of dissatisfaction, I prefer the more active policy implied by the alternative grading of "satisfactory", "satisfactory after adjustment" or "unsatisfactory" (Doughty, 1975). In figure 1 the two attitudes are compared and, although the figures given with both classifications may appear at first sight to be similar, the more active striving after perfection in the second classification would suggest a higher standard of efficacy in that more patients are ultimately satisfied. No extradural should deserve to be categorized as "no benefit", unless the labour has proceeded so rapidly that time did not allow for setting up the block again. I believe, too, that one should examine more closely the reasons why some extradural blocks are unsatisfactory. Many cases can be traced to a human failure, a failure of management, but the remainder, and these should be



Conventional System (Passive)	Fully Satisfied 80	Helped 14	No benefit 6
Proposed System (Active)	Satisfactory 80	Satisfactory after Adjustment 14	Unsatisfactory (a)Management Failure (b)Method Failure 6

FIG. 1. Assessment of efficacy of extradural analgesia.

very few, may be attributed to the intrinsic fallibility of the method.

A breakdown of my personal results (table I) collected from more than 2500 patients shows that approximately three-quarters of them were classified as "satisfactory". These were patients in whom the extradural block was set up and gave complete satisfaction against the background of standard management instructions to the midwives and therefore required no further intervention by the anaesthetist. A further 17% were in the category "satisfactory after adjustment"—in other words, they were salvaged from being unsatisfactory by some further positive action by the anaesthetist, from giving a small extra dose with the patient tilted to one side, to re-siting the cannula in another lumbar interspace. The remaining 7% were unsatisfactory, this impression being gained by observation during labour, at the time of delivery, or by interviewing the patient on the day following delivery.

TABLE I. *Efficacy of extradural analgesia in 2532 patients, 1968–78*

Satisfactory	1920 (75.8%)
Satisfactory after adjustment	430 (17.0%)
Unsatisfactory	
Management failure	104 (4.1%)
Method failure	78 (3.1%)

Let us accept that in perhaps 3% of cases some dissatisfaction can be attributed to the essential fallibility of the method, although most observers would have described these cases as having been "helped". The failures that are preventable are those of *management* (table II), the commonest reason for which was the failure of the midwife to give the top-up punctually or in the correct position appropriate to the site of the mother's pain. Occasionally, the anaesthetist was not called to make the necessary adjustment: the extradural block had been established satisfactorily and yet the subsequent doses given by the midwife did not give adequate relief. Satisfactory analgesia was not restored on 21 occasions, either because the anaesthetist was unavoidably occupied elsewhere or, more frequently, because his help had not been sought by

TABLE II. *Failure of management of extradural analgesia: analysis of 104 patients*

Top-ups not given correctly	76
Anaesthetist not present to make a necessary adjustment	21
Labour progressed too rapidly for the extradural block to become effective	7

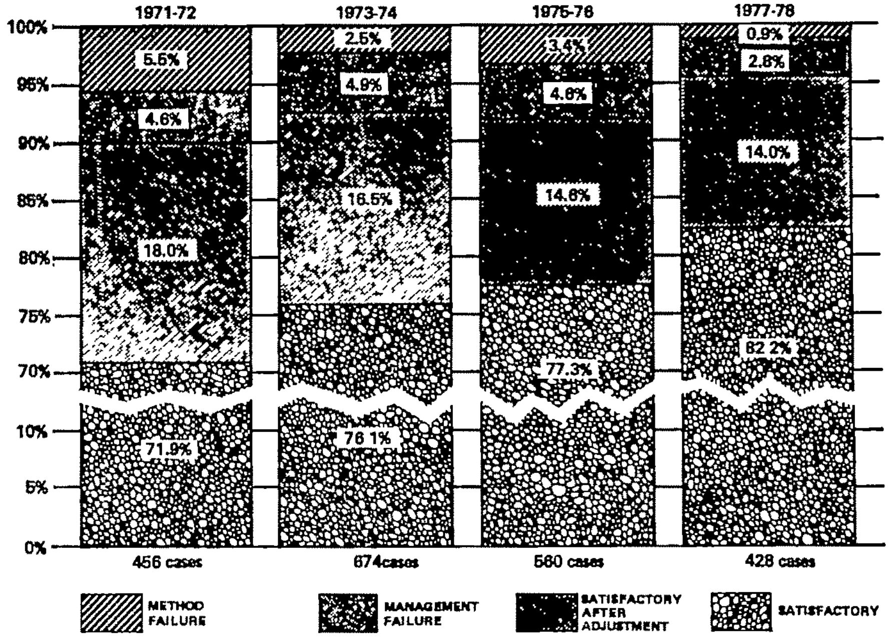


FIG. 2. Change of assessment of efficacy of extradural analgesia with passage of time.

the midwives. On seven occasions the labour progressed too rapidly to give time for the extradural block to become effective. In other words, the anaesthetist was called too late. Although an extradural block should not be attempted when the baby's head is crowning, one should have the confidence to try to give the mother a painless delivery with a single-dose injection even though labour has advanced to the second stage. In these circumstances the ability to be quick and safe is at a premium.

From these figures it will be seen that more than one-half of the failures could have been salvaged by more effective management. These 104 cases, 4% of the total, may be regarded as the casualties of the system in which the anaesthetist is not constantly present in the labour ward.

It might be asked whether the results have improved with continuing experience and advances in technique over the passing years: figure 2 shows that between 1971 and 1976 unsatisfactory analgesia has continued at the rate of 7–8% of all extradural blocks and that these were evenly divided between method and management failure. In 1977–78 a marked reduction in the frequency of failure of the block is shown and a gradual trend can be discerned towards a higher frequency of immediate and sustained success of the analgesia in recent years. While more blocks can now be left in the hands of the midwives without the need for the anaesthetist's intervention, persistent effort in their education is still needed to reduce the chance of mismanagement.

Romine, Clark and Brown (1970) of Arkansas have shown how the efficacy of extradural blocks varies according to the experience of the operator (fig. 3). The senior staff appear to obtain results similar to those that I have just presented. Those obtained by more junior staff underline the importance of very close attention to training and supervision when the service is in the hands of less experienced performers. The senior staff's standards are those which should be maintained and it is therefore the senior staff who should be doing the teaching. In Britain, all too often novices receive their teaching from those with relatively modest competence and short experience.

There exists a prevalent belief that a senior anaesthetist's training obligations are discharged by teaching extradural blocks in the operating theatre against the background of general surgery. This is of limited value, as it must be evident that obstetric extradural analgesia can only be learned in the delivery suite and in harmony with the total obstetric management of the woman in labour.

CONCLUSION

I believe that anaesthetists have a serious responsibility to ensure that extradural blocks are given effectively and safely. Where training and supervision

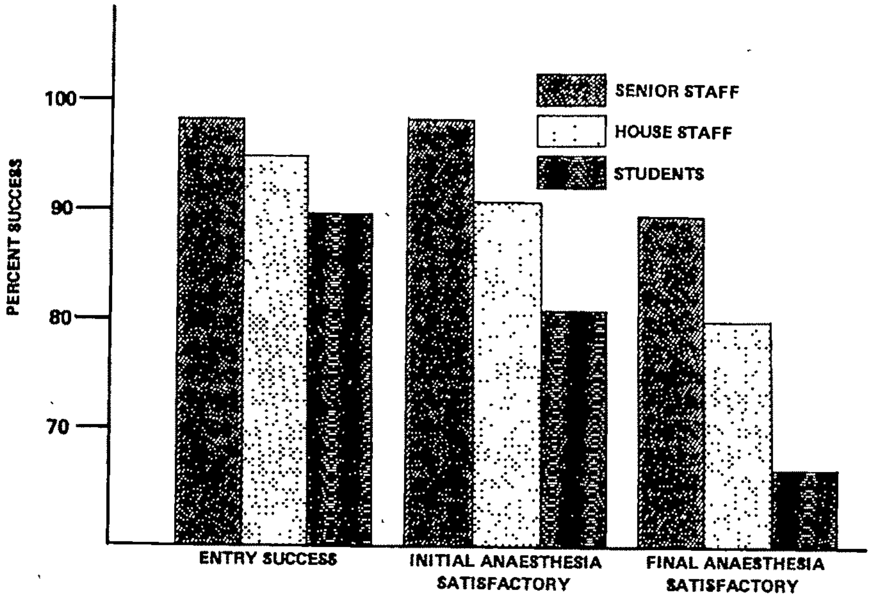


FIG. 3. Success of entry into the extradural space, and initial and final satisfactory quality of anaesthesia by experience of operator (after Romine, Clark and Brown, 1970).

are haphazard, the results can only bring discredit on the method itself. Ineffective extradural blocks, accompanied by a high frequency of complications, deserve adverse criticism.

Unfortunately, the attainment of consultant rank in anaesthesia does not necessarily guarantee the ability of the individual to practise or to teach the technique. There is an overwhelming need for the establishment of advertised instruction courses for those whose hospital appointments do not include opportunities for this experience. Irrational prejudice against obstetric extradural block can only be countered by the eloquence of consistently superb results speaking for themselves, but training must ensure that the unskilled practice of the method does not attract justifiable criticism.

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DISCUSSION

DR ROSEN: Could I take issue with Dr Doughty about who should be allowed to administer extradural blocks. I do not believe that we should train anyone in this technique unless he is fully competent to resuscitate the patient, should a total spinal or cardiac arrest occur. The operator must therefore know the general principles of artificial ventilation, how to intubate the trachea, etc. Dr Doughty emphasized the need to make the technique effective. I would rather stress the question of safety. Patients do not die because of ineffective analgesia, so that the technique must be absolutely safe. Deaths resulting from extradural blockade associated with non-anaesthetists are now due to appear in the next confidential report on maternal deaths in the United Kingdom.

DR DOUGHTY: I did say at the beginning of my talk that I intended concentrating on the teaching of the technique and on ensuring the efficacy of the block. You may be assured that the teaching of safety, the reduction of side-effects and the avoidance of complications is well emphasized during our training course.

CHAIRMAN: I would like to call two speakers to tell us about the percutaneous administration of ketocaine for analgesia in labour. Dr Holmberg, in collaboration with Dr H. Edstrom, has the results of a preliminary clinical study. Dr Åkerman and Dr Berlin-Wahlén will then tell us something of the pharmacology.

DR N.-G. HOLMBERG (SUNDSVALL): Like most painful sensations from the viscera, the pain of uterine contraction is referred pain, felt in the abdomen, groins and low back region (Bonica, 1975). The possibility of obtaining analgesia by interfering with this viscero-sensory reflex might therefore constitute an alternative form of analgesia. Rose (1929), using an intradermal infiltration of procaine during the first stage of labour, managed to achieve analgesia and good results were reported by others (Theobald, 1946; Abrams, 1950).

Local infiltration of the skin of the dermatomes involved is time-consuming for the doctor and unpleasant for the patient. A new preparation (Ane-Pad*) containing a local anaesthetic, ketocaine (fig. 1), in a special vehicle, produces percutaneous local anaesthesia. Dr Edstrom and I have carried out a preliminary study to determine if significant relief of pain could be obtained using these pads.

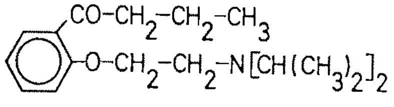

FIG. 1. Ketocaine.

Sixty patients in established labour were studied. Thirty received ketocaine Ane-Pads and 30 were controls, according to a randomized list. The patients were not studied in consecutive order, the majority being patients admitted to the labour ward at periods of relative quiet. Patients who had previous obstetric complications or known allergies were excluded.

The pads are available in air-tight envelopes of plastic-coated aluminium foil and each contain ketocaine 840 mg. When the patient complained of pain, usually at cervical dilatation 3–4 cm, the pads were applied to the skin over the low back, covered by thin plastic foil (to prevent evaporation of the solution) and fastened by surgical tape. The application period was 1 h. We attempted also to apply the pads to the abdomen and groins, but found this impractical.

There was a high proportion of primiparous women in the ketocaine group, but no other important differences between the groups (tables I and II).

During labour a careful record was kept by the midwife, of contractions, cervical dilatation and effacement, fetal heart rate and maternal arterial pressure. Every 30 min an assessment of the pain in the abdomen, groins and back was made by the patient according to a 0–3 pain score.

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* Ketocaine (base) 0.10 g ml^{-1}, isopropanol 0.45 g ml^{-1}, glycerol 0.12 g ml^{-1}, water 0.25 g ml^{-1}, acetic acid 0.001 g ml^{-1}.

TABLE I. *Summary of patient data* (I)

	n	Age ($\bar{x} \pm$ SD)	Parity			Onset of labour	
			0	1	>1	Spontaneous	Induced
Control	30	25.8±4.5	12 (40%)	15 (50%)	3 (10%)	20 (67%)	10 (33%)
Ketocaine	30	25.9±6.0	20 (67%)	6 (20%)	4 (13%)	19 (63%)	11 (37%)

TABLE II. *Summary of patient data* (II). *FHR=fetal heart rate*

	n	Cervix		Contractions (median)	Station present part (median)	FHR ($\bar{x} \pm$ SD)
		cm (median)	Effacement			
Control	30	3	100% :12 (40%) >50%: 8 (27%) 50%: 6 (20%) <50%: 4 (13%)	1/4′	−2	141±6
Ketocaine	30	3	100% :15 (50%) >50%: 7 (23%) 50%: 4 (13%) <50%: 4 (13%)	1/3′	−1	138±10

After removal of the pads, the degree of oedema or hyperaemia, or both, was noted.

Both groups were treated similarly, having access to conventional analgesics (nitrous oxide in oxygen and pethidine 100 mg i.m.). Paracervical blocks or extradural analgesia were not given to either group.

The analgesic effects are shown in figures 2–7. In the control group there were no major changes in pain in the low back after the pain had reached its maximum (figs 2, 3).

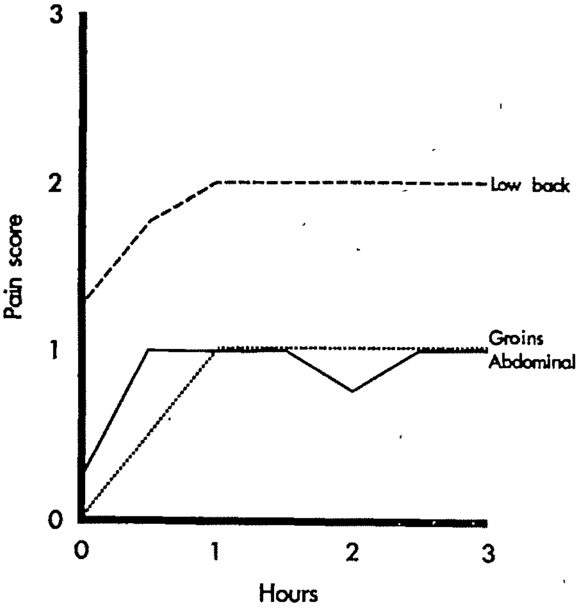

FIG. 2. Pain scores at different time intervals, control group.

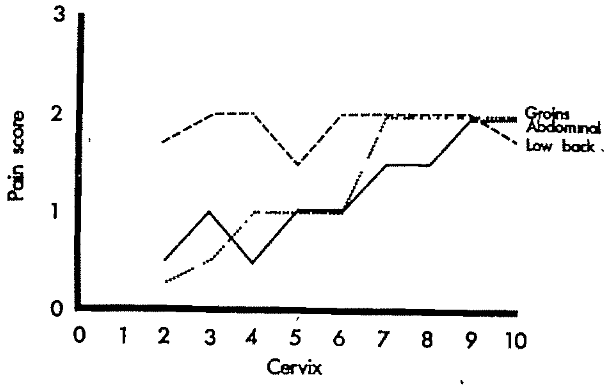

FIG. 3. Pain scores at different degrees of cervical dilatation control group.

The pain seemed to be more pronounced in this region as compared with the abdomen or the groins. Pain developed faster in the low back and reached its full intensity at cervical dilatation 3 cm, compared with the groins or the abdomen, where it reached full intensity when cervix was dilated approximately 6 cm. (The small notch on the low back pain curve in figure 3 was probably caused by the administration of pethidine.)

In the treated group there was a considerable reduction in low back pain, the difference in the pain score between the groups being statistically significant ($P<0.05$), 0.5, 1 and 1.5 h after the start of the investigation (fig. 4) and at cervical dilatation 4, 6 and 7 cm (fig. 5).

It also seems evident, when comparing *individual* changes in pain during labour, that ketocaine has an analgesic effect superior to that of conventional analgesics. Significantly

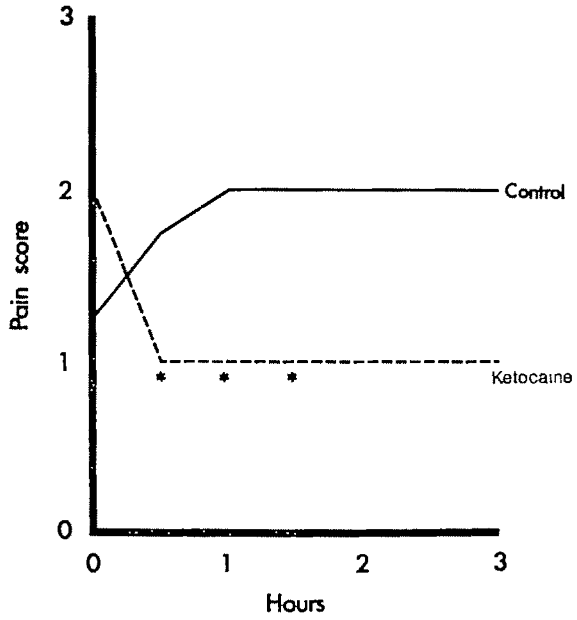

FIG. 4. Low back pain scores at different time intervals.

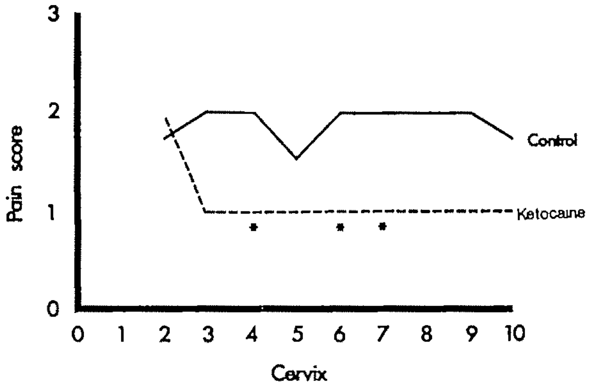

FIG. 5. Low back pain scores at different degrees of cervical dilatation.

more patients said they had less pain in the treated group than in the control group (figs 6 and 7).

Another way of evaluating the analgesia is to compare the consumption of pethidine which is given to women in labour in our clinic. A significant difference was found between the two groups concerning the percentage of patients given pethidine (fig. 8, $P < 0.05$). No difference was found with regard to the administration of nitrous oxide in oxygen.

No differences were found between the groups with regard to the duration of labour (table III). Two neonates in the ketocaine group had Apgar scores less than 7 at 1 min. One patient had a breech delivery with a forceps extraction of the aftercoming head, the other a secondary inertia and delivery by vacuum extraction. Both neonates had an Apgar score of 9 at 5 min. There was no clinical evidence of a deleterious effect of ketocaine on the fetus.

TABLE III. *Duration of labour* (*mean* ± *SD*)

	Duration of labour (min)	
	From Cx 2–3 to 5 cm	From Cx 5 to 10 cm
Control	218 ± 106	127 ± 85
Ketocaine	218 ± 135	150 ± 121

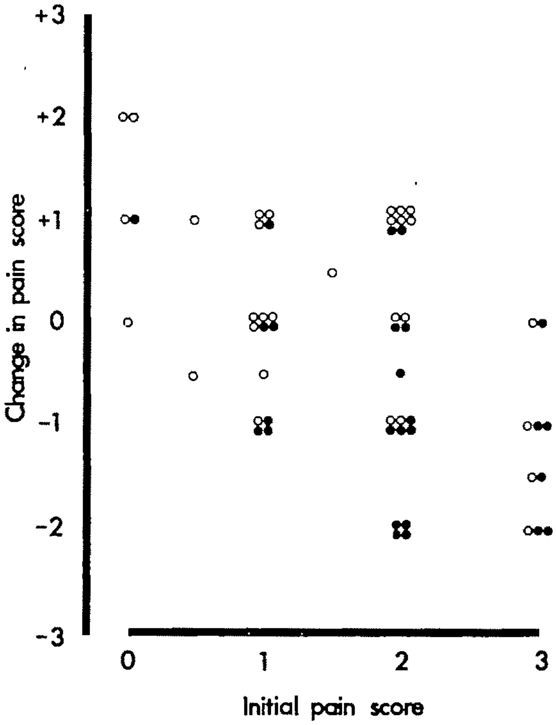

FIG. 6. Individual changes in pain score in relation to initial pain score during the first 3 h of investigation (open circles = control group; filled circles = ketocaine group).

Only very small concentrations of ketocaine ($\leqslant 121$ ng ml^{-1}) have been detected in maternal and fetal blood. In one single case showing a greater blood concentration (278 ng ml^{-1}) the mother suffered from ichthyosis, a fact that might have had an influence on the percutaneous absorption of ketocaine.

No effects from ketocaine were observed on the maternal circulation. There was a slight increase in arterial pressure similar to that found during normal labour.

The most frequent side-effect during application of the pads was a subjective (in most cases comfortable) feeling of warmth. Other effects were itching or burning pain. In most cases these effects were negligible and no severe reactions in the form of hyperaemia or oedema were observed. The hyperaemia was more pronounced than the oedema.

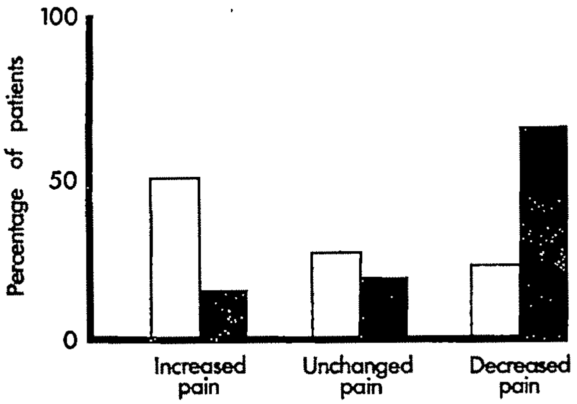

FIG. 7. Changes in pain during the first 3 h of investigation (open bars = control group; hatched bars = ketocaine group).

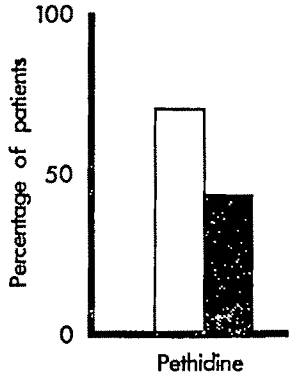

FIG. 8. Percentage of patients given pethidine during the investigation (open bar = control group; hatched bar = ketocaine group).

We wish to emphasize that this was an introductory study, conducted in an open-labelled manner and therefore open to criticism.

The selection of patients for our trial offered practical problems and it was not possible for us to study all patients in a consecutive order. A certain element of bias may be present, the midwives choosing co-operative women arriving at the labour ward during quiet periods; there were more primiparae in the ketocaine group. On the other hand, this serves to enhance our positive results, as it seems probable that the first labour is the most painful (Holmberg, Holmberg and v. Schoultz, 1975).

Another form of bias in evaluating the effects of Ane-Pad concerns the attitude of the midwives. There was a common deep-rooted scepticism against the method, but a general feeling of surprise when the results were presented.

For practical reasons we were only successful in applying pads to the back, and our only analgesic effect was with low back pain. Pain in the abdomen and groins has been relieved by local infiltration of the skin in those regions (Rose, 1929; Abrams, 1950), and our results may be much improved if we could devise a method of applying ketocaine to these areas.

Holdcroft and Morgan (1974) have reported that more than 75% of women in labour obtain little or no pain relief from pethidine, a result that is confirmed by our study. Because of the absence of observable effects on the neonates after the maternal use of ketocaine it seems probable that this method of analgesia compares favourably with the more controversial pethidine in first stage labour.

Our results demonstrate that, by using Ane-Pad, analgesia was achieved in the low back during the first stage of labour. Consequently, Ane-Pad may constitute a useful complement to other techniques of relieving the pain of early labour, and it deserves further investigation.

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DR B. ÅKERMAN (SÖDERTÄLJE): It is well known that the normal, unbroken skin offers a much greater resistance to the penetration of local anaesthetics than do mucous membranes, and attempts by different methods to obtain local anaesthesia by epicutaneous application have met with little success (Monash, 1957; Brechner, Cohen and Pretsky, 1967; Dalili and Adriani, 1971; Rapaport, 1971). The complexity of factors that may be involved in the production of percutaneous anaesthesia has been under study in animals (Åkerman and colleagues, in preparation). The present report concerns an agent, the aminoether ketocaine, which was found to be of potential interest during the search for a specific percutaneous local anaesthetic.

Local anaesthetics of varying structure were studied utilizing the base form of the agents and different solvent media. Gauze pads containing the test solution were applied under occlusive dressings to the shaven backs of guinea pigs. Absence of a twitching of the skin evoked by pricking the treated area with a pin was taken as a criterion for anaesthesia.

Ketocaine was found to be the most potent agent of those tested, irrespective of the vehicle used. It is interesting to note that a mixture of isopropanol and water in such proportions as to achieve an almost saturated solution was at least as effective a vehicle for local anaesthetics as aqueous dimethylacetamide, which was the most effective penetration enhancer for local anaesthetics of a large number of aprotic solvents studied.

Further illustrations of the percutaneous efficacy of ketocaine compared with other agents using 10% saturated solution in the alcoholic vehicle (not shown here) were obtained.

Ketocaine is an aminoether which has been reported to be a clinically effective local anaesthetic agent for parenteral use (Appiani and Laveneziana, 1966) and on mucous surfaces (Filippone and Molinelly, 1967). A high lipid solubility and lack of labile protons capable of forming hydrogen bonds with functional groups in the stratum corneum may be physico-chemical properties of importance for its topical anaesthetic effectiveness.

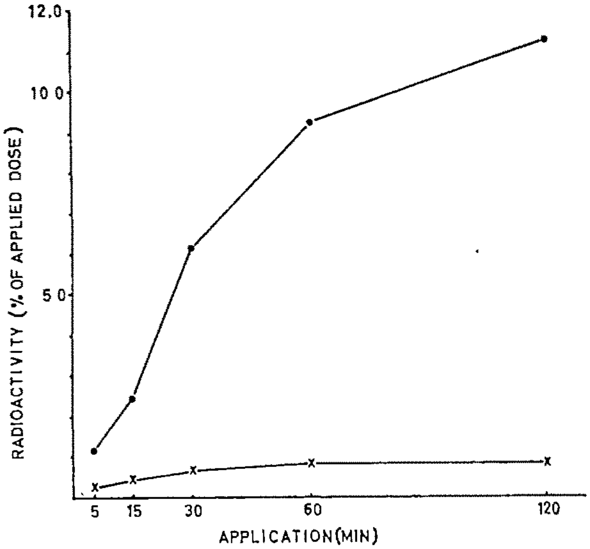

FIG. 1. Radioactivity of skin after application of ^{3}H-labelled ketocaine (upper curve) compared with ^{14}C-labelled vehicle (lower curve) indicating absorption of ketocaine into intact skin.

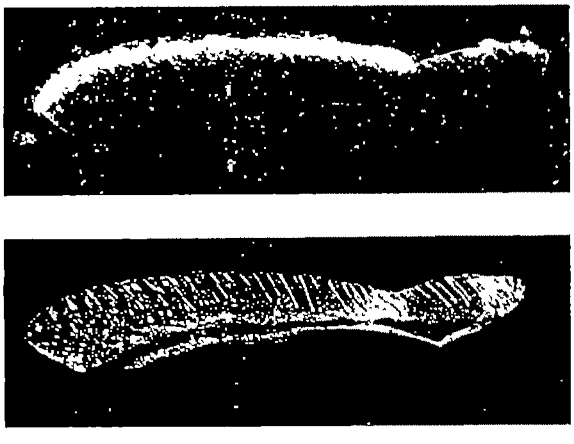

FIG. 2. Autoradiogram of guineapig after 30 min of application of ketocaine to intact skin.

Additional studies were performed with almost saturated solutions of ketocaine in alcoholic (isopropanol) mixtures, while the composition of the solution (A 2358) was investigated in more detail. The solution contained some glycerol to soften and lubricate the skin and a small amount of acetic acid as a stabilizer. Epicutaneously applied, A 2358 gave rise to full anaesthesia of a comparatively long duration after a short contact time. Incisions could be made in the treated area without giving rise to reactions of pain.

The uptake and the distribution of ketocaine in the skin following application of A 2358 were studied using a ^{3}H-labelled compound. The radioactivity in the treated area of the skin increased from about 1% after 5 min application to approximately 11% (upper curve) after 2 h application (fig. 1). The radioactivity in the skin was very low after application of the vehicle only (lower curve) containing ^{14}C-isopropanol. The vehicle itself did not block the twitching response to pinpricking upon epicutaneous application.

Figure 2 consists of an autoradiogram (upper) showing the radioactivity (light areas) in the skin after 30 min application of A 2358 containing ^{3}H-ketocaine in the guineapig and the corresponding sections, as negative prints (lower), stained with haematoxylin-eosin (magnification = ×6.4). The distribution of the radioactivity suggests penetration of ketocaine both via hair follicles and through the epidermis. According to other autoradiograms the total amount of ketocaine and the depth of penetration increased with the time of application.

These findings indicate penetration of ketocaine to levels in the skin where nerve fibres are present, in order to exert a local anaesthetic action.

The percutaneous anaesthesia produced by ketocaine was reversible, suggesting no damage to nervous tissue. No signs of systemic toxicity were recorded in these studies. In studies on animals it has been shown that the acute toxicity of ketocaine is somewhat greater than that of lignocaine (Setnikar, 1966). The subcutaneous LD_{50} in mice for ketocaine has been given as 217 mg kg^{-1} and for lignocaine, 260 mg kg^{-1}. The i.v. LD_{50} values were 14 mg kg^{-1} and 25 mg kg^{-1} respectively. Other toxicity studies also predict adequate safety for ketocaine and A 2358 (Flodh and colleagues, in preparation).

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DR A. BERLIN-WAHLÉN (SODERTÄLJE, SWEDEN): The systemic absorption of ketocaine following epicutaneous administration has been studied in volunteers. For this purpose, a mass fragmentographic method was developed, which made possible the determination of blood concentrations accurate to about 5 ng ml^{-1} (Berlin-Wahlén et al., 1977).

The blood concentrations following epicutaneous administration were compared with those following brachial plexus block, where 30 ml of a 1% solution of ketocaine hydrochloride was given to 10 patients undergoing routine surgical procedures. After brachial plexus block, maximum blood concentrations were obtained after 30 min in six of 10 patients and ranged between 1.01 and 2.59 µg ml^{-1}. The mean total body clearance was 0.2 litre min^{-1}, which is about one-third of that reported for bupivacaine (Tucker et al., 1977). In five subjects, when three pads, each containing 840 mg of ketocaine base, were applied on the thigh under occlusion for 3 h, the blood concentrations did not exceed 0.30 µg ml^{-1}.

The influence of dose and application time on the systemic absorption of ketocaine has been investigated in a cross-over study in six volunteers (fig. 1) where three or six pads were applied for 3 or 9 h (Berlin-Wahlén et al., 1979). Both the doses and the application times in this study considerably exceed those intended for routine clinical use. The greatest individual blood concentration observed in this study was 1.27 µg ml^{-1}.

Estimation of the degree of systemic absorption was based on comparison between the areas under the blood concentration *v.* time curves. Assuming 100% bioavailability after brachial plexus block, the systemic absorption following epicutaneous application was less than 2% of the total amount in the pad (table I).

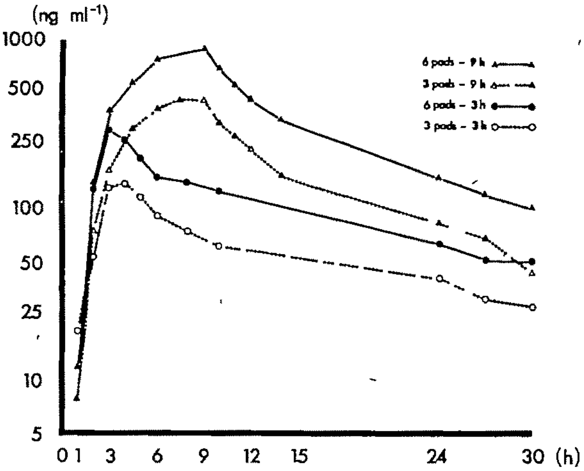

FIG. 1. Mean blood concentrations of ketocaine following epicutaneous administration in six volunteers.

There were no adverse effects on the e.c.g. during the application, after removal of the pads, and 24 h later (L. Rydén, personal communication).

After repeated application in the same skin area, persistent hyperaemia was observed in one of the subjects. Local side-effects such as hyperaemia and vesicle formation can occur after repeated application in the same skin area.

TABLE I. *Estimated amount of ketocaine absorbed into the systemic circulation following epicutaneous administration of A 2358*

No. of pads	Application time (h)	Estimated amount absorbed	
		mg	% of total
3	3	14	0.55
6	3	26	0.52
3	9	43	1.70
6	9	85	1.68

Several minor metabolites have been identified in rats, including N-dealkylated, side chain and ring hydroxylated and conjugated biotransformation products (Berlin-Wahlén and Sandberg, 1977).

Whole-body autoradiography in mice indicated that ketocaine is rapidly distributed to adipose tissue, lung, kidney and urinary bladder, liver, gall bladder and intestinal contents following i.v. administration of ^{14}C-labelled compound. Such a distribution pattern indicates extensive enterohepatic circulation, and it has been shown in rats that 55% of an i.v. administered dose is excreted into the bile within 3 h (Berlin-Wahlén and Sandberg, 1977).

Following i.v. administration in pregnant mice, very low amounts of radioactivity were found in the fetus as compared with the mother (Bodin, Malmfors and Ramsay, 1979) (fig. 2). Moderate concentrations were found in the placenta and amnionic sack, but no specific localization in fetal tissues occurred.

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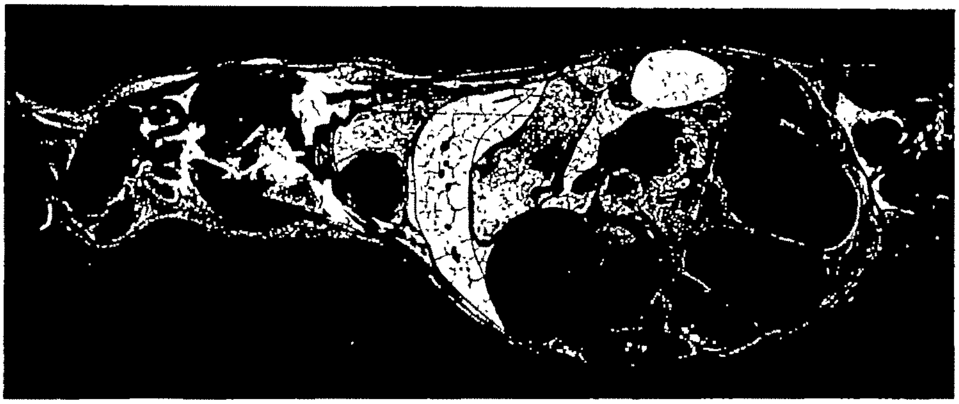

FIG. 2. Distribution of ^{14}C-labelled ketocaine in the pregnant mouse 15 min following i.v. injection of 11 μmol kg^{-1}.

DR GORDH: When I carried out the pilot study using ketocaine for percutaneous local anaesthesia, I obtained relief of labour pain in 80% of the mothers tested. Is that the sort of figure you were getting?

DR HOLMBERG: About 70–75% of our patients claimed to have a decrease in their pain following the institution of skin anaesthesia, with the pads. So I think the figures are very comparable.

DR DIFAZIO: Do you know if the drug is a systemic analgesic? There is the possibility that it was absorbed through skin and acted centrally.

DR HOLMBERG: I cannot say for sure, but the blood concentrations we measured were extremely low.

DR SCOTT: The drug has been used for ordinary nerve blocks and the blood concentrations in such cases were some 15–20 times that measured by Dr Holmberg. If the drug were a systemic analgesic at the much lower concentration, one would expect considerable side-effects if the concentrations reached 20 times that level.

DR DIFAZIO: It could be that the drug had a plateau effect such that increasing the dose did not increase its effect. However, I agree with you that this is probably unlikely. When given for a brachial plexus block, how long is the duration of local anaesthesia?

DR BERLIN-WAHLÉN: In the study I referred to, the half-life of the drug was about 35 h and it was cleared at a rate of 0.2 litre min^{-1}, which is about one-third of the rate of clearance of bupivacaine.

DR B. COVINO (FRAMINGHAM, MASS.): The original reports on the drug that came from Italy seem to indicate that it lasted slightly longer than lignocaine, but not as long as bupivacaine or etidocaine.

DR SCOTT: Many of the patients to whom this drug was applied developed an erythema at the site of application and this apparently is not the common type of erythema that one finds in irritation. Could I ask Dr Juhlin, who is a dermatologist, to elucidate this point for us?

DR L. JUHLIN (UPPSALA): The degree of erythema that you see is related to the time of application. Thus the redness may be only just visible after 1 h, but will usually be well marked 3 h after application. It disappears within 24 h. With Drs Haegerstam and Evers, I measured the temperature on the treated areas. Normally one would expect an area of erythema to have a greater temperature. However, this is not the case with ketocaine; the temperature, in fact, decreased when erythematous areas became more marked. The only explanation we can offer for this observation is that the erythema is passive and there is a stasis on the venous side.

If the patient's skin is not completely intact, then the erythema is often much more marked. Blistering can occur in such cases. We have also seen some cases of sensitization where repeated application of the pads caused more and more erythema, and blistering.

DR SCOTT: It seems that this agent can produce skin anaesthesia sufficient enough to allow the painless taking of split skin grafts. Whether or not the anaesthesia of skin in the area of referred pain is effective in alleviating labour pains is another matter. Dr Holmberg's study seems to indicate that it might well do this, but the final word must be left until the completion of a controlled double-blind study.

It is very important that mothers are informed regarding the various available methods of pain relief in labour sometime during their pregnancy. Could I ask Dr Poppers from the New York Medical Center how he goes about this in his practice?

DR P. J. POPPERS (NEW YORK): An important element in the management of obstetric anaesthesia is the preanaesthetic education and evaluation of the patient. All too often, the administration of anaesthetics to the woman in labour is made difficult by a lack of patient co-operation and an equally disturbing lack of preparedness on the part of the anaesthetist. We have initiated a programme with a dual aim: to prepare the obstetric patient for anaesthesia during her labour and delivery and to establish a preanaesthetic evaluation record that contains sufficient data for the anaesthetist. For this purpose, a standard form has been designed for recording the history and physical examination. It is used for both private and clinic patients, and is completed during a personal interview.*

The record contains a brief but pertinent history. Obstetric risk factors, such as toxaemia, arterial hypertension, general cardiovascular and respiratory abnormalities and haemorrhage are listed. Drug history, allergies and drug reactions are recorded. Drug addiction, with its very serious physical consequences, is common enough to be a regular part of the history. In view of the preponderance of extradural anaesthesia in our obstetric service, spinal abnormalities are investigated routinely. Details of the course of previous pregnancies and obstetric and surgical anaesthesia are listed.

The physical examination includes auscultation of heart and lungs. The arterial pressure is measured with the patient standing, lying on her back, and positioned on the left side. Routine laboratory data are obtained by the obstetrician, but a relatively high frequency of pulmonary and neuromuscular disease often necessitates lung function tests in addition.

The therapeutic measures listed include advice regarding food intake when the expected day of confinement is near, and when labour has actually begun. The most important aspect is a discussion of obstetric anaesthesia, and the recommendation and explanation of a specific course of action. The response of the patient is recorded. Finally, the recommended management is carefully noted to assist the anaesthetist in caring for the patient when she is admitted to the hospital.

Before the interview, the private patient is given a letter during a prenatal visit, which explains the different methods of obstetric pain relief, including the natural childbirth technique, systemic medication, extradural block, and inhalation anaesthesia. It describes the activities of the obstetric anaesthetist, including his involvement in infant resuscitation, adds a precautionary note about food intake, and finally requests the patient to make an appointment with the obstetric anaesthetist on duty. At that interview, the antenatal record is completed, and a preliminary plan for anaesthetic management made and explained.

The clinic patient, in our hospital, presents a different challenge. Her physical status is, on average, not as good as that of the private patient. The care for our clinic patients may be complicated further by great anxiety and a lack of communication because of a serious language barrier and, on occasion, limited intelligence. Distribution of written material to such patients would most likely fail in its purpose. Personal explanation and reassurance are needed. This has made it desirable for us to assign a resident anaesthetist to the obstetric clinic, to interview and examine every patient in the third trimester. The resident completes the antenatal anaesthesia record, with the assistance of an appropriate interpreter if necessary. In consultation with the staff anaesthetist on duty, he develops a plan for management that covers different eventualities. The written anaesthetic evaluation becomes part of the regular patient record. It is immediately available to the anaesthetist when the patient is admitted to the labour ward.

Experience has shown that this approach to patient education and evaluation facilitates anaesthetic management. The patient seems to accept and even welcome it. She knows what to expect and the anaesthetist has appropriate guidance in deciding upon the definitive management, even if he had not seen the patient before. The interview also proves to be extremely valuable in dispelling in the patient false ideas about the effects and dangers of obstetric anaesthesia, notions that are implanted by the lay press, misinformed friends or poorly informed obstetricians.

To the members of the perinatal team, it appears to be a valuable part of the overall care of the patient. To the anaesthetist, in particular, it constitutes a major contribution to a successful outcome.

Dr Rosen: In Cardiff we deliver about 6000 babies a year, all in two hospitals. Only about 50% of mothers attend parentcraft classes and we are trying to devise ways of increasing this figure. Our basic aim is to allow each mother to choose the type and the degree of analgesia that she would like. This philosophy is agreed also by all our consultant obstetricians and midwives. The anaesthetist explains to the mothers attending the parentcraft classes the various methods of analgesia available, including psychoprophylaxis. Most mothers make an effort to learn psychoprophylaxis, although only 3% sustain it throughout labour without the addition of other forms of analgesia. They are told that pethidine will relieve pain but seldom makes it disappear completely and will make them sleepy. They are informed about inhalation agents and how they relieve pain. Again, it is emphasized that total pain relief is not to be expected. About 70% of mothers use these methods during labour. Extradurals are given to about 25%, and mothers are told that extradurals are the only method by which total relief is likely to be obtained. They are informed that this method increases the forceps delivery rate especially in primiparae. They are also warned about the possibility of headache following accidental lumbar puncture, which occurs in about 1–2% of our extradural blocks, stressing the important fact that it will eventually go away. Having made her choice of the analgesic method the mother is reassured that she can change her mind during labour and choose another more effective method.

For the 50% who do not attend mothercraft classes, we know that approximately one in five of them cannot read properly. It is useless to give such patients written handouts and we are investigating the use of learning machines and incentive games to improve their knowledge.

We try to see all patients after the onset of labour to explain again the methods available and to seek their permission to use them. We stress to our midwives and doctors that it is just as wrong to give a patient an analgesic which she does not want as it is to withhold analgesia from a mother who does want it.

Dr K. Strasser (Dusseldorf): I would like to raise the question of the test-dose in extradural blocks. In our clinic over the past 5 years we have performed approximately 1500 extradural blocks in obstetric practice and are convinced that in one case we were able to prevent a total spinal anaesthetic by using a test-dose. The dose we used was 6 ml of 0.25% bupivacaine and this caused a very high level of anaesthesia.

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* Copies of the form may be obtained by application to Dr P. J. Poppers, Department of Anesthesiology, New York University School of Medicine, New York, N.Y. 10016.

Dr Scott: Opinions about the test-dose are of course divided, and taking the people in this room we seem to be divided about 6 to 4 between those who do and those who do not use a routine test-dose.

Dr G. Willdeck-Lund (Uppsala): Ihave to tell Dr Strasser that the dose he uses for a test-dose is the same as we use for the main dose. Our first injection never exceeds 6 ml of 0.25% bupivacaine.

Dr E. Lindbaek (Oslo): We not only give a test-dose initially, but before each top-up as well. Our dose is 8 ml of 0.25, 0.375 or 0.5% bupivacaine and when this is being given by the nurse anaesthetist or occasionally by the midwife, we tell her to give half of it with the patient lying on one side followed a few minutes later by the other half given on the opposite side.

Dr Scott: What may be more important in preventing high spinal anaesthesia, especially during a top-up dose, is the question of catheter design. There was a recent death, reported by Ward and colleagues (1978), in a surgical patient receiving continuous extradural block. Cardiac arrest and eventual death occurred at the third injection down the catheter, in spite of the fact that on each occasion a test-dose had been given. The authors carried out *in vitro* tests on the catheter which was a blind-ended Portex catheter with two side holes. If the distal hole was inserted into a bag of saline and the proximal hole left outside, injection with a moderate amount of pressure caused the injectate to exit through the proximal hole, that is, in the clinical situation, into the extradural space. If more pressure was used on the syringe then most of the injectate came out through the distal hole, that is into the bag of saline. In a clinical situation this might well produce a high spinal anaesthetic. It may well be, therefore, that high spinals occurring during top-up injections are due to the fact that the catheter was originally inserted into the subarachnoid space, but one or both of the side orifices was still in the extradural space. This therefore raises the question as to whether only catheters with a single terminal orifice should be used.

As the question of safety has now been raised in this discussion, could I remind you that a few years ago the Association of Anaesthetists of Great Britain and Ireland asked all its members to report to them confidentially any neurological complications occurring during and after extradural block. Dr Doughty was associated with that enquiry, and I would ask him therefore if he could present the results of it to us now.

Dr Doughty: Six years ago the Association of Anaesthetists asked for reports of neurological sequelae associated with spinal and extradural block (Lee, 1972). Some 90 reports (table I) were sent to and assessed by Dr L. Hargrove of the Westminster Hospital, London; publication is still awaited, so what I have to say must be regarded very much as a preliminary communication. Only 59 of these cases were related to obstetrics and not all the complications reported could be classified strictly as neurological. For example, there were three cardiac arrests with two deaths in the course of extradural block induced for Caesarean sections. All three injections were given by the same anaesthetist. The two deaths might have been avoided if the resuscitative measures had been carried out more competently. Two other patients developed neurological deficits after Caesarean section. In one case the disability lasted for only 7 days; the other case was diagnosed as anterior spinal artery thrombosis and there remained some degree of upper-motor neurone damage 5 years later.

Fifty-four cases were reported following extradural block for the relief of pain in labour. Some were due to errors of technique such as dural puncture and trauma due to catheter or needle. Some cases were assessed as probable obstetric trauma. In 14 cases it was very difficult to attribute the lesion either to the extradural block or to the obstetric procedure, owing to poor documentation or transient disability. There was a residuum of eight cases in which there appeared to be a direct relationship between the neurological damage and the extradural block.

Table I. *Summary of indications for anaesthesia*

(A) Extradural blocks	
Relief of pain in labour	54
Anaesthesia for Caesarean section	5
Anaesthesia for other surgery	12
For relief of chronic intractable pain	5
Insufficient information or very transient disability	10
(B) Subarachnoid blocks	
For operative surgery	4
Total	90

The question must be raised, therefore, as to whether or not there is a risk inherent in the technique regardless of the competence of the person carrying it out. Certainly there is an impression that neurological complications are extremely uncommon in centres where anaesthetists skilled in extradural block are working and where the training of juniors is meticulous. In his classic monograph on the subject, Usubiaga (1975) concluded that neurological sequelae of extradural block were few and in most instances were preventable.

Dr Albrecht: Could you tell me from how many cases of extradural block were the 90 cases collected?

Dr Doughty: I regret that we do not know the number of extradurals that are given in the United Kingdom or what proportion of these 90 reported cases represent the total number of neurological and other complications that have actually occurred.

Dr DiFazio: Do you know how many cases who developed neurological deficit experienced parasthesiae during the injection?

Dr Doughty: There were certainly some cases who had parasthesiae during the injection and these were classified as needle and catheter trauma and therefore were probably preventable.

Dr Brautigam: The term "massive extradural" has been used in the literature. Could you give us indication of how common it is?

Dr Doughty: This term was introduced by Dr Massey Dawkins (1969) who reported that some patients had developed a very high block and had to be ventilated because of the onset of apnoea. Boys and Norman (1975) ascribed subdural injection of local anaesthetic to a case in which a similar clinical picture evolved of a very high block with a rather slow onset, but without apnoea. Radiological evidence showed that the catheter was in the subdural space and they suggested that subdural injection may be the explanation of the so-called "massive extradural". Personally, I have seen three similar cases without apnoea, but without radiological confirmation.

Dr Scott: It should be remembered that extradurals do extend to high levels on occasions. In doing our double-blind study reported to you by Dr Littlewood, we were obliged to use the same volume of solution in every case, namely 10 ml and this could sometimes produce blocks up as high as T3.

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CONCLUDING REMARKS

Dr Covino: Regional anaesthesia is now almost 100 years old. It was in 1884 that Kohler first used cocaine installation for ophthalmology. Regional anaesthesia for obstetrics, however, is still rather new. We heard this morning about the pathways involved in the production of pain during labour. There was some discussion also regarding the advantages and disadvantages of no analgesia *v.* centrally acting analgesics *v.* local anaesthesia. In the second section we heard about the possible effects of drugs on the neonate, both acute and chronic, and how these might possibly be measured by neurobehavioural studies. It is impossible to say at this time what is the significance of the neurobehavioural changes that are sometimes seen. Instead of waiting for the outcome of the long-term studies into this problem, is it reasonable to undertake a retrospective study into children born with and without regional anaesthesia 10 years ago? I know that in Sweden, for instance, they have an excellent system for following the progress of their citizens from birth to the grave. Perhaps they may be able to use these data to answer these important questions. There is a tendency in obstetric anaesthesia to worry about the psyche of the neonate but perhaps we worry too little about the psyche of the mother. What psychological harm is done by a very painful labour?

Looking to the future, it is my belief that we require our more scientific studies in obstetrics. There is a great deal of clinical experience and clinical opinion, but extremely little hard scientific data. For example, on the question of which drug to use for extradural block in labour, Dr Littlewood has presented one of the very few double-blind studies in obstetrics, but this is the kind of information we require.

We have also to recognize the differences in obstetric practices from country to country if we are to appreciate what is going on world-wide. Only if we understand each other's problems will we be able to use each others' experience and knowledge to our own advantage.

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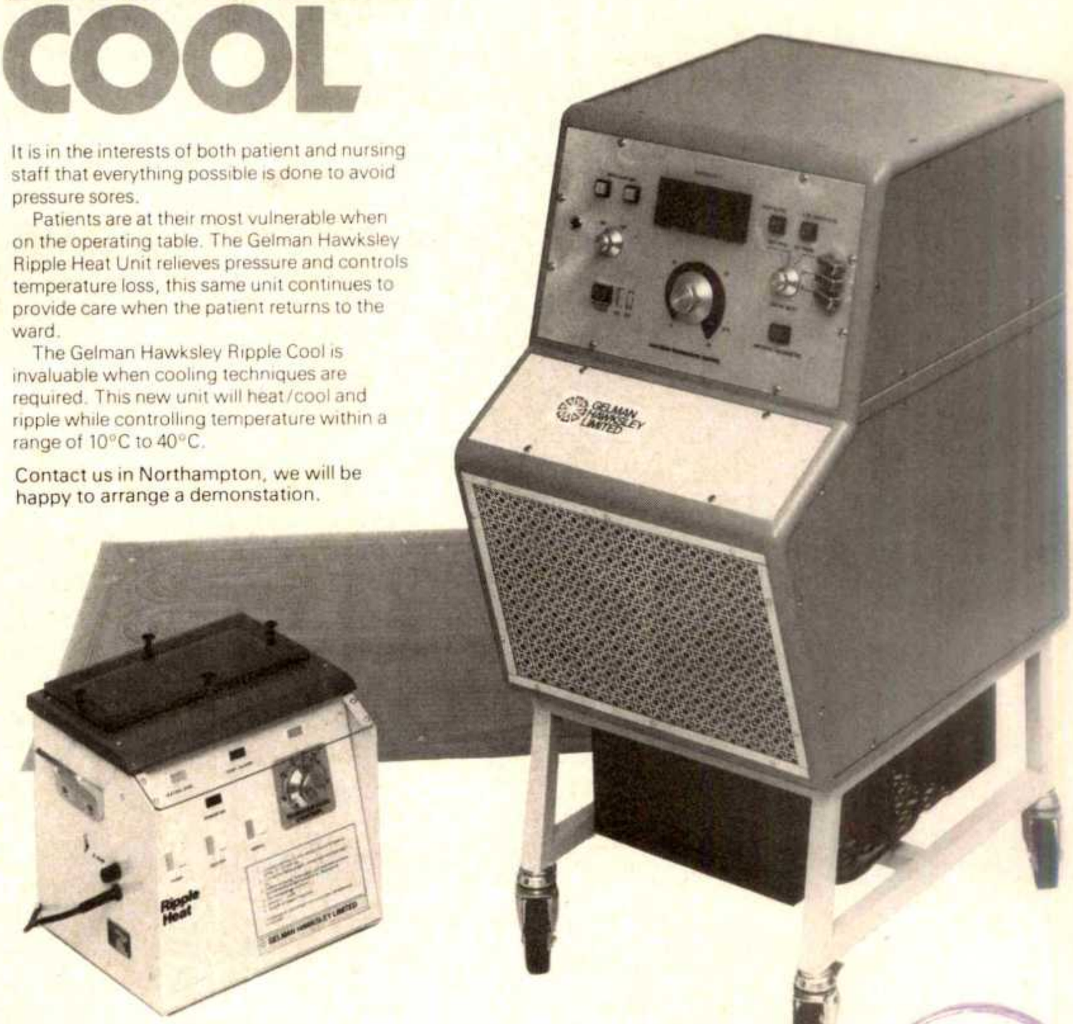

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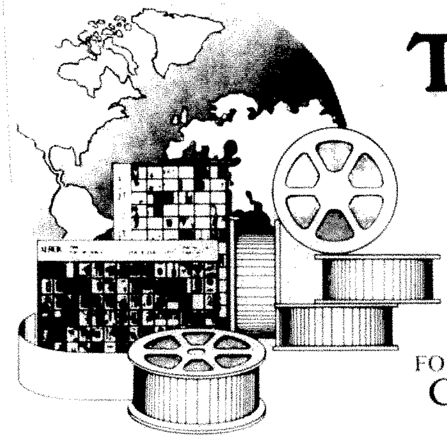

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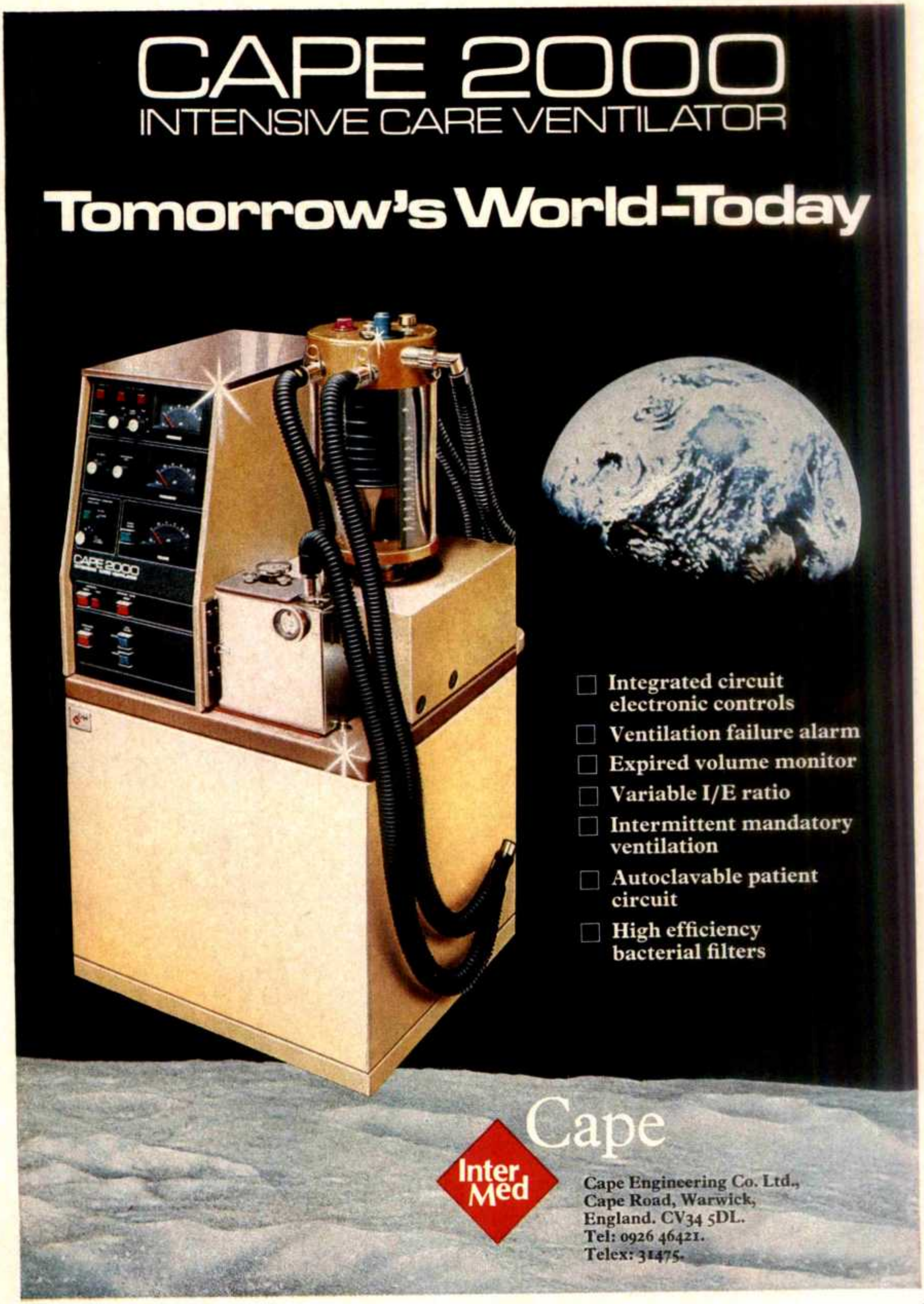

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Trasylol may in very rare cases (less than 0.1%) cause hypersensitivity reactions.

Presentation
Ampoules of 100,000 KIU (Kallikrein Inactivator Units)
Ampoules of 200,000 KIU*
*not available in the Republic of Ireland

PL0010/5900

1) Schneider et al., Chirurg **47,** 185 (1976)
2) McMichan et al., Med. Welt **27,** 2331 (1976)

General information

Instructions to the printer. Words to be printed in lower-case italics should be indicated by one underline. Two underlines indicate small capitals, three indicate large capitals and four, italic capitals. A wavy underline indicates a word to be printed in bold type.

Headings in the text. Six possible grades are available:

1.	PART I	(capitals)
2.	RESULTS	(small capitals)
3.	Blood-gas analysis	(l.c. roman)
4.	*The action of drugs*	(italics, centre)
5.	*Lung function studies*	(italics, full out)
6.	*Volume.* Large volumes. . . .	(italics, indent)

Symbols and Abbreviations. In accordance with Editorial adoption of SI Units, abbreviations and symbols should follow the conventions described in the booklet "Units, Symbols and Abbreviations. A Guide for Biological and Medical Editors and Authors" (ed. G. Ellis), published by and available from The Royal Society of Medicine, 1 Wimpole Street, London, W1M 8AE. Words for which abbreviations are not included should be written in full at first mention in the summary and again in the text and followed by the abbreviation in brackets. This will usually be in the form of large capitals without separating points.

Spelling, etc. British spelling should be used with "z" rather than "s" spelling in, e.g. organize, organization.

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It is proposed that a proportion of the Journal be devoted to correspondence each month. Every effort will be made to ensure that correspondence arising from papers in a recent issue is published without delay, and for this reason, relevant correspondence will be given priority over that pertaining to original research. Authors of correspondence concerning original work will receive proofs at the Editor's discretion.

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BRITISH JOURNAL OF ANAESTHESIA

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EDITORIAL

IMMUNOLOGY IN ANAESTHESIA AND INTENSIVE CARE

In recent years developments in the understanding of the immune system and its disorders have touched almost every aspect of medicine, often providing insight into hitherto inexplicable phenomena.

General anaesthesia causes depression of the immune system. Although there is some experimental evidence that this could enhance the spread of tumours, whether anaesthesia *per se* is important in this respect in man is debatable. Were a consensus of opinion to accept that general anaesthesia is important in the spread of tumours, then whenever possible it would have to be avoided in patients with malignant disease undergoing surgery. However, if the view, expressed by Walton in this issue (p. 37), that the endocrine response to trauma is more important in promoting tumour spread is accepted, then it could be argued that suppression of this response, either by large doses of opiates or by block of afferent impulses with local anaesthesia, is indicated in these patients. On theoretical grounds the current practice of light general anaesthesia would appear to offer the worst of both worlds, not only by depressing the immune system but also by failing to obtund the endocrine and metabolic response to trauma.

It is difficult to believe that the transient changes in the immune system caused by a short period of anaesthesia in the routine surgical patient are of any consequence providing there is no malignancy or risk of serious infection. Much more important are the acute adverse immune-mediated reactions to drugs, blood, blood substitutes and other substances administered by anaesthetists. Such reactions may kill an otherwise healthy patient undergoing a simple surgical procedure.

Patients suffering from diseases involving the immune system may develop crises associated with cardiorespiratory failure. These patients need intensive care and supportive techniques, such as artificial ventilation and occasionally aortic balloon pumping, for their short-term survival. However, they also require that those in charge of their care have a knowledge of the possible diseases involved so that the appropriate therapy, such as plasma exchange and immunosuppression, is introduced in time to ensure a satisfactory outcome.

In most immunological disorders the responses may be classified according to whether they are mediated predominantly by antibodies or by lymphocytes. In each case the response can be classified according to the type of antibody or lymphocyte involved. The sites of the response and its clinical features may also assist in classification.

One of the most widely used classifications was introduced by Gell and Coombs (1962) in which responses involving antibodies are classed into types I, II and III, while cell-mediated reactions are called type IV. *Type I reactions* are called anaphylactic. They include hayfever, asthma and some drug reactions. The presence of an antibody (immunoglobulin usually of type E (IgE) and in some instances IgG) sensitizes mast and other cells (for example, in the lungs). A subsequent challenge by the antigen causes the release of chemical mediators (for example histamine, slow reacting substance of anaphylaxis, eosinophil chemotactic factor, thromboxanes, and a variety of amines and peptides) which affect capillary permeability and smooth muscle tone causing rashes, urticaria, oedema of the airways, bronchospasm and cardiovascular collapse. *Type II reactions* are those in which antibody and complement cause damage by attaching to antigens on the surface of cell membranes. Transfusion reactions and haemolytic anaemias fall into this group. The antibodies are of two main types. IgM causes complement fixation to erythrocyte membranes and the complement then "punches" holes in the membrane, leading to cell lysis. Antibodies of the IgG type cause red cells to be destroyed by phagocytic cells in the reticuloendothelial system. *Type III reactions* in these immune complexes are formed between soluble antigens and antibodies. "Serum sickness" is an example and can be caused by the repeated injection of foreign serum proteins. Following the injection, for example, of horse anti-tetanus serum, circulating antibodies to horse proteins form immune complexes in the circulation and when these settle in the walls of blood vessels they induce an inflammatory reaction which involves neutrophils. *Type IV, cell-mediated reactions* include delayed hypersensitivity reactions, graft rejection and some types of autoimmune disorders.

In the current issue of this journal a number of articles have been assembled to provide a basis for understanding the immunological problems which sometimes occur in anaesthetic practice and intensive care, and to indicate, where possible, some of the potentially desirable future developments in therapy.

J. G. Whitwam
J. Norman

REFERENCE

Gell, P. G. H., and Coombs, R. R. A. (1962). *Clinical Aspects of Immunology*. Oxford and London: Backwell Scientific Publications.

ERRATA

ANAESTHESIA FOR STUDIES OF THE CEREBRAL CIRCULATION: A COMPARISON OF PHENCYCLIDINE AND ALTHESIN IN THE BABOON

Br. J. Anaesth., **50**, 985

Sir,—I must apologise sincerely for a mistake which I have only just noticed in the above article.

Page 985, Col. 2, line 7: The dose of phencyclidine should be "(approx. 0.07 mg min^{-1})" and not "(approx. 0.67 mg min^{-1})" as printed.

W. Fitch
Glasgow

A PHARMACODYNAMIC MODEL FOR PANCURONIUM

Br. J. Anaesth., **50**, 1113

Sir,—In the appendix to our recent paper we presented a series of formulae for the general solution of a three-compartment open model (equations 8–16). We regret that these equations contain a sign error, in that where the initial drug concentration $C_1(0)$ appears in these equations, it is entered as a positive quantity. It should be entered as a *negative* quantity. Those readers who wish to use these formulae (8–16) should therefore change $C_1(0)$ to $-C_1(0)$ in each instance.

C. J. Hull

Br. J. Anaesth. (1979) **51,** 3

THE IMMUNE SYSTEM—SOME BASIC CONCEPTS

J. J. T. Owen

Immunology is all about recognition; recognition of what is foreign as opposed to what is self. It is to do with how the body perceives invading organisms and reacts to the antigens they contain so that under normal circumstances we are able to survive in a hostile environment. However, these days the subject has become of far greater importance than simply a matter of self-defence. As a by-product of the defensive reaction we react to and reject foreign transplants. Under certain circumstances, we over-react to foreign antigens and symptoms and manifestations of hypersensitivity or allergy ensue. Sometimes "self" tissue is recognized as foreign and auto-immune processes are initiated. Thus the subject of immunology has broad implications in medicine both in situations which are beneficial and in situations with adverse consequences. In addition, there is the possibility that immune responses may be elicited to cancers and that ultimately this may be used to therapeutic advantage.

First let me return to the question of recognition. The number of foreign antigens that we can recognize and respond to is large if not limitless. Synthetic substances not found in nature may elicit an immune response on injection into the body. Yet each foreign antigen elicits an immune response which is specific to it and we are presented with a daunting question, namely how is it that we are able to produce so many different specific antibodies to combat all of the various antigens which may enter the body? The origin of this diversity of immune responsiveness is a problem which has intrigued immunologists for many years and various theories have been proposed to account for it.

What seemed at the time a most reasonable theory suggested that each antigen determined the structure of the specific antibody to it by acting as a template or pattern on which the structure of the antibody might be moulded. Thus, according to this notion, cells produce antibodies which are not specific but which become specific for an antigen after they have been moulded to a complementary shape by contact with the antigen. Unfortunately this idea, although seemingly reasonable, turned out to be erroneous and its acceptance at the time thwarted the development of immunology for many years. A major turning point came with the insight that the structure of antibody molecules is not determined by contact with foreign antigens, but is encoded in the genetic apparatus of cells so that a "library" of antibody molecule "types" is produced in the embryo before foreign antigen has been encountered. This idea is the kernel of the Clonal Selection Theory which now forms a basis for much of our thinking in immunology.

Clonal selection—the basis of diversity of immune responsiveness

The insight of clonal selection is the notion that a cell (and the cells involved in the recognition of antigen are lymphocytes) can respond to a foreign antigen only if it possess an antigen recognition receptor specific to that antigen. We know that the molecules which recognize and combine with antigens are antibody molecules and therefore it is proposed that antibody molecules on the surface of cells act as antigen recognition receptors. Indeed, the clonal selection theory holds that each lymphocyte is unispecific and has on its surface antibody molecules of only one "type" or "specificity", so that each cell can recognize and respond to one or only a few related antigens. Thus the broad range of foreign antigens which may enter the body are recognized by a repertoire of lymphocytes, each of which is specific for a particular antigen. When an antigen encounters a lymphocyte displaying a recognition receptor complementary to it, the cell is triggered to respond by proliferation and to form a clone, that is a group of cells each derived from the same precursor. If the triggered cell is a B lymphocyte, the cells of the clone will secrete large amounts of antibody of the same specificity for antigen as that of the recognition receptor on the triggered lymphocyte. However, some cells of the clone may not secrete antibody but may persist as long-lived cells to constitute an "immunological memory" which can be re-activated at a later

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date on introduction of the same antigen into the body.

Lymphocytes—central cells in immune responses

One of the basic concepts of immunology is the notion that lymphocytes are crucial cells in immune responses in that they are "immuno-competent" cells, that is they are the cells which recognize and specifically respond to foreign antigens. For many years lymphocytes were thought of as end-cells and so of little importance. However, in the late 1950's it was shown that lymphocytes could be stimulated by antigens to proliferate in tissue culture. At the same time, it was shown that when animals are depleted of lymphocytes by drainage of cells via a thoracic duct fistula they fail to respond to a variety of foreign antigens as well as to tissue grafts. Furthermore, immune responsiveness can be restored in these animals by transfusion of lymphocytes and if the transfused lymphocytes are obtained from an animal which had been either immunized with an antigen or rendered tolerant to an antigen, the properties of immunity or tolerance are conferred on the reconstituted host. In parallel with these findings was the demonstration that lymphocytes are not static cells but are in continuous circulation through the body from the blood, through lymph nodes into lymph vessels and then back to blood vessels via the thoracic duct. This re-circulation of lymphocytes provides an obvious means of ensuring that invading organisms are encountered by lymphocytes with receptors which recognize the antigens of the pathogens.

Two types of lymphocytes—T and B cells

In the early 1970's it was discovered that lymphocytes fall into two major categories, B cells and T cells. B and T cells are morphologically identical and are about equally numerous. They differ, however, in where they are produced and in their roles in immune responses. T cells are generated in the thymus from precursors which migrate to this organ through the bloodstream from blood-forming organs such as fetal liver of the embryo and bone marrow of the adult. These precursors or stem cells enter the framework of the thymus and they undergo extensive proliferation and eventually emerge as T cells capable of reacting in immune responses.

B lymphocytes, on the other hand, are generated within haemopoetic organs themselves; thus in the embryo B lymphocytes are formed in the fetal liver from precursor cells about which relatively little is known. In the adult, B cells are formed in the bone marrow, probably following a period of considerable proliferation in a precursor cell population.

T cells and B cells both possess antigen recognition receptors on their surface which are specific for particular antigens as predicted by the clonal selection theory. However, only B cells have quantities of antibody molecules on their surface which can be readily detected. Indeed until recently, it has been questioned whether or not T cells do recognize antigens by means of antibody receptors, but most opinion supports the notion that they possess at least those portions of antibody molecules which specifically interact with antigen (the variable regions). Nevertheless, only B cells secrete large quantities of antibody following stimulation by antigen; in other words, only B lymphocytes are precursors of plasma cells. T cells, when stimulated, may give rise to clones of cells playing important roles in immune responses by regulating the activity of B cells ("helper" or "suppressor" T lymphocytes) or by acting as "cytotoxic" lymphocytes capable of destroying foreign target cells in grafts or virus-infected cells. In addition, T cells produce factors which can activate other cells, for example macrophages, to participate in immune responses. Thus, the categories of T and B lymphocyte represent an important division of labour in the immune system; B cells playing a major role in what is often known as humoral immunity (that is, immunity primarily dependent on the function of antibodies), whereas T cells play a role in cell-mediated immunity (that is, immunity primarily dependent upon the action of cells). However, this division is not exclusive and, as I have mentioned, T cells play an important part in regulating humoral immunity.

Antigens and antibodies

Antigens are molecules which may be on the surfaces of viruses or pathogenic organisms and which are recognized as foreign by the body. Pathogenic organisms may have a number of regions on their surfaces which are separately recognized by antibodies and these areas are known as antigenic "determinants" or "epitopes". Antibodies are protein molecules consisting of two identical heavy (H) polypeptide chains and two identical light (L) polypeptide chains. The antibody molecule is shaped like the letter Y and it is only the terminal portions of the arms of the Y which are concerned in the recognition of and combination with antigen (the variable regions). This recognition is dependent upon unique sequences of amino acids which in turn confer a unique shape to this portion of the molecule—a shape which must be complementary to that of the antigen in order for combination to take place. The remaining portions of the antibody molecule consist of chains in which the sequences of amino acids are relatively constant from molecule to molecule—hence these are known as the constant regions of H and L chains. However, a variety of classes of antibody have been characterized (IgM, IgG, etc.). The classes are distinguished from each other primarily on the basis of differences in the constant regions of H chains. Each antibody molecule has either a κ or a λ type of L chain.

The interaction of antigen and antibody leads to the formation of a complex between the two, but the attachment is reversible and the strength of attachment depends upon how good is the fit between the shape of the combining site of the antibody molecule and the shape of the antigen to which it has attached. Thus one antibody molecule may be capable of combining with more than one antigen, but the strength of combination will vary. Thus the repertoire of lymphocytes, each with a specific receptor for antigen, can cope with the huge variety of antigens which may enter the body.

Where does the information for the construction of antibodies come from?—genes and mutations

This is an important and intriguing question which follows from the clonal selection theory. It is possible to envisage that there may be a sufficient number of genes in each lymphocyte to code for all of the sequences of amino acids found in the variable portions of antibody molecules. Thus, all the information may be present in the "germ line" of an animal and selected portions of this information may be expressed in each "unispecific" lymphocyte. However, this idea presupposes an enormous number of genes coding for antibodies and recent studies in molecular biology suggest that a sufficient amount of information is not available in the mammalian embryo. Thus, current notions tend to the view that, whilst a certain amount of information for the construction of the variable regions of antibody molecules is present in the DNA of germ cells, a greater variety of information is generated by genetic mutations. These probably occur during the differentiation of lymphocytes, either in ontogeny or during the continuous production of lymphocytes in adult life, which takes place in the thymus in the case of T cells and in the bone marrow in the case of B cells.

What happens when B lymphocytes encounter antigens? —switches and networks

I have already indicated that when a B lymphocyte encounters antigen which it recognizes, it is triggered to proliferate and mature to form a population of antibody secreting cells (plasma cells) making antibody of the same specificity for antigens as on the triggered lymphocyte. What about the question of the class of antibody secreted? It is known that the class of antibody determines, to a large extent, the biological functions of the particular antibody molecule, for example the IgM class of antibody is efficient at cell lysis and the IgE class is involved in allergic reactions. The question arises as to how antibodies of different classes (that is, having different heavy chains) share the same specificities for foreign antigens. Current evidence suggests that, in part at least, this is produced by a so-called "switch" mechanism in which the B lymphocytes, which are first formed during ontogeny and which are known to make IgM antibody, switch to make antibody of other classes during the process of B lymphocyte maturation. They do so without changing the specificity of the molecules on their surface for antigen, but manage to change the class of antibody produced by switching on new genes coding for the constant region of the heavy chains. This process seems not to depend on antigen stimulation. The matter is complicated, however, by the fact that, before antigen stimulation, most B lymphocytes have antigen recognition receptors which are either IgM or IgD, or both. Hence in addition to the "switch" which is independent of antigen there must be a further "switch" during the immune response itself. Thus a lymphocyte which initially has on its surface IgD may switch to produce a clone of cells making IgG antibodies of the same specificity. The precise significance of IgD, which is present in low concentration in the serum and yet is represented on most lymphocyte surfaces, is a matter of active investigation. Some workers believe that it is concerned with whether or not a B cell is switched off (that is, made tolerant to antigen IgD −ve cells) or switched on (that is, rendered immune to antigen IgD +ve cells).

Even this account of the way in which B lymphocytes are triggered by antigen is an over-simplification of the complex control mechanisms which probably operate in the body. Certain, we know that T lymphocytes regulate the activity of B cells. Helper T lymphocytes are required for many B cell responses to antigen and suppressor T lymphocytes are important in regulating the level of immune responses and indeed in preventing B cells reacting against an individual's own antigens. The manner in which antigens are presented to B lymphocytes (and here we have to consider the role of macrophages, which are important in processing and presenting antigen to lymphoid cells) may determine whether B cells respond or not.

Yet a further complication which has been brought to our attention recently is the fact that antibody molecules themselves make good antigens. Even the variable portions of antibody molecules are antigenic and these antigenic regions are known as idiotypes. The point of importance is that, when a particular B lymphocyte responds to an antigen by proliferating to produce a population of cells each making antibody of identical specificity, this specificity, which is determined by the variable portion of the antibody molecule, can be recognized as "different" by other B cells of the same individual. Thus the fact that an individual produces so many diverse antibodies which can be recognized as antigens by other B lymphocytes in the same individual produces a situation likened to a network where interactions may take place between a whole variety of lymphoid cells. Therefore as one B lymphocyte responds and proliferates, its activity may be controlled by the antibody produced by another B lymphocyte which recognizes the first antibody as different. This forms the basis of what is known as the "network" hypothesis.

What happens when T lymphocytes respond to antigen? Role of the MHC complex

As mentioned previously, T cells are now known to exist as a variety of subsets, all produced within the thymus but differing in function and in certain surface markers which allows their separate identification. Major categories are helper, suppressor and cytotoxic cells. Much recent research effort has gone into the characterization of the antigen recognition receptor on T cells and recent work suggests that, in part at least, the recognition process is dependent upon the variable portions of antibody molecules comparable to the system of B lymphocytes. However, T cells seem to recognize antigen in a special way, and this brings me to the role of the major histocompatibility gene complex (MHC) and its products in immune reactions.

Interest in the MHC arises from studies of graft rejection, where it has been shown that the major antigens responsible for transplantation failures are cell-surface antigens coded for by genes of the MHC complex. In man, the MHC complex is located on the short arm of chromosome 6 and more than four important loci can be distinguished. Dozens of alleles of these loci are known to exist in man and therefore it is rare for two individuals to possess identical sets of these genes. T lymphocytes are particularly good at responding to antigens that are presented on cell surfaces. Recent research suggests that T lymphocytes recognize antigens in association with MHC antigens. Thus, T cells will kill cells infected with virus only if these cells display viral antigens in association with "suitable" MHC antigens. In this context "suitable" MHC antigens are those which are present in the thymus in which T lymphocytes have differentiated. These results, which suggest that T lymphocytes may "see" antigen in a complex way, may explain why the possession of certain MHC genes in man determines susceptibility to a variety of diseases.

CONCLUSION

In this short survey I have tried to pinpoint some of the recent major advances in basic immunology which may have "spin off" for clinical work. We know that lymphocytes play a central role in immune responses and although T and B lymphocytes arise and differentiate by separate developmental pathways their ultimate function is interdependent. In addition, both types of cell are "unispecific" in the sense that each lymphocyte is programmed to react to one or only a few antigens. While the antigen recognition receptor contains variable regions of the immunoglobulin molecule in both cell types, T lymphocytes recognize antigen only when it is associated with products of the major histocompatability locus. Regulation of the immune response is an important area of current investigation and is now seen to depend upon a complex network of interactions involving many different cell subsets. Ultimately, our better understanding of these networks is bound to be of importance in attempts to regulate the immune response in disease states.

Br. J. Anaesth. (1979), **51**, 7

THE COMPLEMENT SYSTEM

B. D. Williams

The existence of the complement system was first recognized at the end of the 19th century by the ability of serum to enhance the destruction of bacteria and the requirement of a heat-labile serum factor necessary for the lysis of red cells. Since then extensive research by many groups of workers led to a detailed understanding of the structure, activation sequence and biological importance of this system. It consists of a group of plasma proteins whose sequential interaction may be initiated by immunoglobulins, microbial products and proteolytic enzymes. Activation is achieved by the generation and assembly of highly specific enzymes and is accompanied by limited proteolytic cleavage; this leads to the release of biologically active peptides and the formation of large multimolecular complexes.

The complement system may be divided into four functional sections, two pathways for activation (the classical pathway and the alternative pathway), an amplification mechanism for augmenting the activating pathways and a final common effector pathway to which the activating sequences are directed and from which the biological activities are derived (fig. 1).

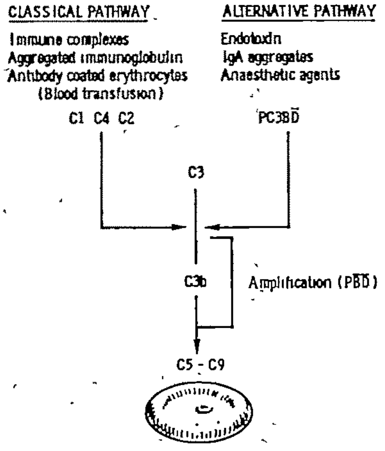

Fig. 1. When activation of the classical pathway is initiated by antibody-coated erythrocytes and activation proceeds through to the terminal components a characteristic complement lesion is visible on the red cell surface.

The proteins of the classical pathway are signified by C and a number designates the complement component (C1, C4, etc.). The activated state of a component is indicated by a bar over the number, for example, C$\bar{1}$. Cleavage fragments are suffixed with letters, for example C3a and C3b, while an inactive fragment is denoted by i—C3bi.

A provisional nomenclature for the alternative pathway factors uses letters rather than numbers, but it maintains all other conventions used for the classical components. The approximate molecular weights, electrophoretic mobilities and serum concentrations of the complement components and factors are shown in table I.

Classical pathway of complement activation

This pathway consists of three components: C1, C4 and C2. Activation can be initiated by antigen-antibody complexes, and aggregates of IgG1, IgG2, IgG3 and IgM. Binding and activation of C1 has also been shown to occur with C-reactive protein complexed to pneumococcal type C polysaccharide and to polyanion–polycation complexes such as heparin-protamine complexes. C1 consists of three subcomponents, C1q, C1r and C1s and these form a large multimolecular complex in the presence of calcium ions. Binding of C1q to the CH_2 domain of aggregated immunoglobulin will activate C1r, which in turn acts proteolytically on the C1s subunit. The activated C$\bar{1}$s cleaves its natural substrate C4 into a low molecular weight fragment C4a and the larger fragment C4b binds to the aggregate, or to the cell membrane if activation is triggered by membrane-bound immunoglobulin, via a nascent binding site. This reaction enhances the efficiency of C$\bar{1}$ and leads to more efficient cleavage of C4 and also cleavage of C2. This component is also cleaved by C$\bar{1}$ and the binding of a major fragment of C2, C2a, to C4b forms the classical pathway C3 convertase—C4b2a. This enzyme undergoes a temperature-dependent decay with a half-life at 37 °C of 5–10 min. Loss of

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TABLE I. *Properties of the complement components and factors*

	Molecular weight	Electrophoretic mobility	Serum concn (μg ml^{-1})	Cleavage fragments
Classic pathway				
C1q	390 000	λ2	190	
C1r	188 000	β	*	
C1s	110 000	λ2	120	
C4	209 000	β1	430	C4a, C4b, C4c, C4d
C2	117 000	β2	30	C2a, C2b,
C3	210 000	β1	1300	C3a, C3b, C3c, C3d
C5	206 000	β1	75	C5a, C5b,
C6	95 000	β2	60	
C7	120 000	β2	*	
C8	163 000	λ1	*	
C9	79 000	λ	160	
Alternative pathway				
B	100 000	β2	240	Bb, Ba
D	23 500	λ	1–5	
Properdin P	223 000	λ2	25	
Control proteins				
C$\overline{1}$INH	105 000	λ2	180	
C3b INA (KAF)	100 000	β2	25	
B1H	150 000	β1	450	

* Not known.

activity is associated with the release of the C2a fragment, now designated C2i, from the convertase.

The alternative or properdin pathway

It is now well established that C3 conversion can also occur via a pathway which is independent of the early classical pathway components. Early experiments defined a role of properdin, a serum protein which formed a complex with yeast cell-wall polysaccharide at 17 °C, and in the past 7 years intensive analysis has defined the proteins involved in C3 activation and the mechanisms by which this is achieved. Activation can be produced by IgA aggregates, inulin, zymozan, endotoxin and aggregates of the F(ab')$_2$ fragment of IgG. The only cation required for activation is magnesium, and activation occurs most efficiently in concentrated serum. The expression of this pathway is dependent on a positive feedback mechanism in which C3b, the major cleavage product of C3, interacts with two other proteins, B and $\overline{D}$, to generate an additional C3 convertase. These reactions are summarized in figure 2. C3b is capable of forming a weak association with B, but the complex formed has only a limited ability to cleave more C3 molecules. However, cleavage of B to Ba and Bb, and the association of the latter fragment with C3b results in the generation of another C3 convertase, C3b Bb. This convertase, the alternative-pathway C3 convertase, is very much more efficient in producing C3 cleavage and the C3b produced by this reaction is now available for the further production of a C3 convertase, so creating the positive feedback nature of this pathway.

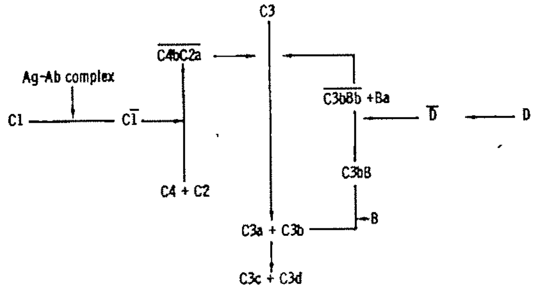

FIG. 2. Complement activation to the C3 stage by the classical pathway and the feedback loop for C3 activation.

As well as providing the C3 convertase of the alternative pathway, the C3 feedback serves as an amplifying system for activating the complement system from C5 to C9. Decay of the alternative pathway convertase is also rapid (half-life 4 min at 30 °C), and the loss of enzyme activity is related to the loss of Bb from the convertase. What is not clear about the alternative pathway activators is the precise way in which they initiate C3 conversion. The most popular view is that properdin stabilizes the labile C3b Bb convertase which has been assembled on the surface of zymozan particles. The C3b necessary for combination with B probably arises from the continued low grade activation of the classical pathway or by proteolytic cleavage of C3 by enzymes such as plasmin.

Once C3b has become bound to the classical C4b C2a convertase it further modifies this enzyme so that it now acquires additional specificity for C5. It cleaves this molecule to produce a small fragment, C5a, and the larger fragment C5b interacts with C6 to form C5b6 and begins the assembly of the multimolecular C5–C9 complex. The reaction of C5b6 with C7 leads to the formation of C5b67, on the cell membrane; C5b6 in the fluid phase can also react with C7, forming C5b67, which is, for a short period of time, capable of binding directly to the cell surface in the absence of antibody or the earlier complement components. Finally, the C5b67 complex interacts with C8 and then C9, completing the formation of a multimolecular C5–C9, capable of damaging the cell membranes. Before considering the factors regulating the activity of the complement system, the following statements may help remove some of the confusion generated by this subject.

(a) The C3b feedback pathway and the alternative pathway are not synonymous. The feedback pathway is the C3 converting system which is utilized by the alternative pathway.

(b) The C3b feedback pathway can be activated by the classical and alternative pathways. Breakdown or utilization of the alternative pathway components cannot therefore be used as evidence to indicate alternative pathway activation.

(c) Activation via the classical and alternative pathways are not mutually exclusive.

Regulation of complement

Two general mechanisms limit the extent of complement activation.

The first is inherent and is represented by the rapid decay rates of the enzymes C3b Bb and C4b C2a and this consequently restricts activation of C3–C9. The labile membrane binding sites of C3b and C5b also limit the cytolytic effect of the complement system. The second mechanism is extrinsic and is exemplified by the C$\bar{1}$ inhibitor (C$\bar{1}$INH), and C3b inactivator (C3b INA) and B1H. C$\bar{1}$ INH controls the assembly of the classical pathway convertase by binding to the C$\bar{1}$s subunit and irreversibly inhibiting its capacity to cleave C4 and C2. The C3b INA serves as a major control protein of the complement system by converting C3b into two inactive fragments, C3c and C3d. Loss of haemolytic activity precedes fragmentation and the latter may be facilitated by the presence of non-complement proteases. Genetic deficiency of C3b INA is associated with hypercatabolism of C3, B and D because of the uncontrolled generation of C3b Bb. B1H initiates extrinsic decay dissociation of Bb from C3b Bb even after this convertase has been stabilized by properdin and it also accelerates C3b inactivation by the C3b INA. These two controlling mechanisms—intrinsic decay of a labile convertase, displacement of Bb from the convertase with B1H and inactivation of C3b by the C3b inactivator—are shown in figure 3. C3 Nef, an immunoglobulin present in the serum of some patients with hypocomplementaemic mesangiocapillary glomerulonephritis, can overide all of these controlling mechanisms because it prevents the B1H displacement of Bb from its binding site on C3b. Since the C3b INA cannot inactivate C3b while it is complexed to Bb, convertase activity persists, the feedback pathway is activated and the result is persistently low concentrations of C3.

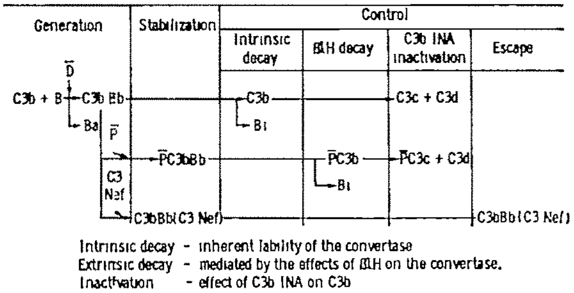

FIG. 3. Amplification phase of complement activation, generation, stabilization and control of amplification C3 convertases (Fearon et al., 1976).

Biological activities of complement

Complement activation produces fragments and complexes of complement components which may be directed against foreign proteins or the host's own tissues. These effects are summarized in table II.

Activation of C2 leads to the generation of a kinin-like moiety (C2a) which causes vasodilatation and increases vascular permeability. Anaphylatoxin activity is provided by C3a and C5a and these components and the trimolecular complex C5b67 are chemotactic for leucocytes. C3 conversion produces leucocytosis and C3 itself plays a role both in the

Table II. *Biological effects of complement* (*Lachmann*, 1975)

Adherence reactions	
C3 "Immune adherence" to primate r.b.c. and non-primate platelets "opsonic adherence" to macrophytes and polymorphs	Important in phagocytosis and allergic inflammation
Induction of some thymus-dependent antibody responses	
Induction of memory cells	
Solubilization of immune complexes	? modulate degree tissue damage

Active fragments	Vaso active	Histamine releasing	Chemotactic
C2	+		+
C3a		+	+
C5a		+	+
C567			+
Membrane lesions	C5–C9 Lysis of r.b.c., w.b.c. and platelets Lysis of nucleated cells Lysis of micro organisms		

induction of an immune response to certain thymus-dependent antigens and in the generation of memory cells. One of the most important biological activities of C3 is that of C3b in producing immune adherence: macrophages have C3b and C3d receptor sites which take up C3b and C3d when they are bound to bacteria or immune complexes. The binding of C3b to such complexes considerably enhances their phagocytosis. The most dramatic effect of the complement system, but not its most important, is membrane lysis. A recent finding which may be important in regulating the tissue-damaging effects of immune complexes is the ability of the complement system to solubilize large antigen–antibody complexes.

Since the most important biological effects of complement are consequent upon the breakdown of C3, inherited deficiencies of this component or acquired deficiencies as a result of the absence of important regulatory proteins such as C3b INA are associated with repeated bacterial infections. Deficiencies of other components in humans and animals are almost always without ill effect, although in man, deficiency of the early components C4 and C2 is often associated with a lupus-like syndrome.

Under certain circumstances, activation of the complement system can be of considerable disadvantage to the host and may initiate rather than prevent tissue damage. In cytotoxic reactions complement is frequently involved, and the red cell destruction following incompatible blood transfusions or thrombocytopenia following sedormid are two such examples. Complement is also involved in producing glomerular damage in nephrotoxic nephritis and the mechanism involves the fixation of C3 and the attraction of polymorphs by chemotactic factors. Complement is also intimately concerned in the production of immune complex disease. Changes in vascular permeability produced either by IgE-mediated reactions or by anaphylotoxin are important in localizing the complexes to the vessel wall. The attraction of polymorphs to the site and their retention by adherence reactions initiate the mechanisms which produce tissue damage.

Clinical investigation of complement function

(1) *Abnormal concentrations of individual complement components.* It is possible to measure the total haemolytic activity of serum, and antigenic and functional assays are also available for the components of the classical and alternative pathways (Lachmann and Hobart, 1978). Since the activation products of the complement components are removed very rapidly from the circulation, the net effect of intense complement activation is a reduction in the serum concentration of that component. When activation is less intense, a compensatory increase in the rate of synthesis of the protein (many of the complement components are acute-phase proteins) will mask any reduction in the serum concentration of that protein. Although low concentrations are taken to mean

increased catabolism and consumption of that component, it must be emphasized that decreased synthesis can produce the same result, either alone or in conjunction with hypercatabolism.

Measurements of C3 in serum provide a good example of the difficulties involved. The concentration of this protein is influenced by a number of acute-phase stimuli such as surgical operations, trauma and infection and its synthesis may be severely impaired in both acute and chronic liver disease. To determine, therefore, whether decreased concentrations *in vivo* are the result of hypercatabolism, or if normal concentrations of C3 are associated with hypercatabolism, it is useful to demonstrate C3 breakdown products in the circulation. Of the two products produced, measurement of C3d is most useful, since this component persists for a longer time in the circulation than C3c (Perrin, Lambert and Miescher, 1975). It is important, however, to avoid generating artefacts either during the collection of the sample (when activation of the complement system can be prevented by collecting blood into EDTA 0.01 mol litre^{-1}) or during storage. Changes in the concentration of C3 in association with complement activation have been described following the use of the anaesthetic agent alphaxalone (Althesin) (Watkins et al., 1976). If activation occurs *in vivo*, then measurement of the classical and alternative pathway factors provides additional information on which pathway is being utilized.

(2) In vivo *turnover studies of complement components.* Turnover studies of purified, radiolabelled complement components allow calculation of the rates of synthesis and catabolism of these proteins. These studies provide more information than that given by the concentration of a single protein.

(3) *C3 splitting activity in patients' sera.* Some abnormal sera contains factor(s) capable of breaking down the C3 in normal human serum *in vitro*; the factors presumably operate *in vivo*, contributing to the hypocomplementaemia and hypercatabolism. Factors operating via the classical and alternative pathways have been described (Williams et al., 1974).

(4) *Complement components in diseased tissue.* The demonstration by immunofluorescence of individual complement components, often in association with immunoglobulin, provides circumstantial evidence that these components have played a part in generating tissue damage.

Patterns of complement abnormality found in disease are: (a) Specific isolated deficiency of a complement component. Characteristically, one component is totally absent from the serum, and total haemolytic activity is therefore absent also. Other components are present in normal concentrations.
(b) Classical pathway activation. The concentrations of early acting components of the classical pathway C1, C4 and C2 are reduced; low concentrations of C3 are also found, but not out of proportion to the other components. These changes are seen characteristically in SLE.
(c) Alternative pathway activation. Concentrations of C14 and 2 are normal, while those of C3, B, $\bar{D}$ and the late-acting components are low. Activation of the complement system by Gram-negative bacteria produces this pattern.

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AUTOIMMUNITY AND AUTOIMMUNE DISEASE

A. J. REES

Few subjects in clinical medicine cause as much confusion as autoimmunity. Part of the problem is semantic; terminology is muddled, sometimes contradictory and diseases with different pathogeneses and very different clinical features are often grouped together. A less easily remedied source of trouble is ignorance; only in the past few years have advances in basic immunology found application in clinical practice. Even now major scientific and clinical problems are distinct. More information about the control of the immune system is essential before fundamental questions about the origin of autoimmunity can be answered. Pressing clinical questions concern the need for better diagnostic techniques and for more effective means of controlling fulminant disease.

In an attempt to remove some of the difficulties, the purpose of this review is two-fold. First to consider experimental data, because these provide the foundations not only of current practice but also of future developments, and second to describe the investigation and clinical features of some autoimmune diseases, emphasizing those that present difficulties for anaesthetists, either because of their fulminant nature or because they cause particular respiratory problems. Before this, a few words on terminology are desirable.

Terminology (*table I*)

Strictly the term "autoimmunity" should be reserved for immune responses, either cellular or humoral, which are directed against host tissue. Such responses are not always harmful, for instance anti-myocardial antibodies are frequently present after myocardial infarct, but rarely cause injury. In other circumstances autoantibodies may be positively beneficial and Jerne (1973) has even suggested that antibodies (anti-idiotypic antibodies) directed against other antibodies may have an important role in regulating the immune response.

TABLE I. *Classification of autoimmunity.* (*Cell-mediated response is not included because its role in autoimmune disease is uncertain*)

Auto-antibody responses	Normal, e.g. anti-idiotypes Pathological, e.g. α GBM α thyroid
Immune complex disease	Endogenous antigens, e.g. SLE Exogenous antigens, e.g. PAN with Hepatitis B
Unknown mechanism	e.g. Scleroderma Dermatomyositis

Autoimmune disease, then, refers to the harmful effects of autoantibodies. Many such antibodies have been described, antithyroid antibodies, anti-platelet antibodies and antibodies to glomerular basement membrane (GBM) being a few examples.

Unfortunately, in clinical practice, autoimmunity has assumed a wider meaning and has been extended to include certain immune complex diseases, such as polyarteritis nodosa (PAN) and systemic lupus erythematosis (SLE). In these, injury is thought to occur at sites where complexes of antigen and antibody are deposited in the walls of blood vessels. In some instances, complexes consist of host antigen (DNA in the case of SLE) combined with a true autoantibody, whilst in others the antigen is foreign, hepatitis B antigen found in some patients with PAN being an example. However, the antigen responsible has been identified in very few cases and in most, there are no clues to its origin.

Even more confusing is inclusion of diseases such as scleroderma and polymyositis under the umbrella of autoimmunity, as their pathogenesis is uncertain; some have suggested they are caused by cell-mediated autoimmunity, but this is controversial.

It will be apparent by now that many of the diseases under discussion have previously been grouped together as collagen, collagen–vascular or connective tissue disease; these descriptive terms are innaccurate and best avoided.

Development of autoimmunity

Harmful autoimmune responses are unusual. When

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considering why, three questions must be answered: first, what normally maintains unresponsiveness (tolerance) to the host's own antigens? Second, how do autoantibodies arise? Third, how do autoantibodies produce injury?

Tolerance (Weigle, 1973; Dresser, 1976). The first coherent ideas about tolerance were developed by Burnett towards the end of the 1950's. He suggested that lymphocytes which were capable of reacting with self antigens were eliminated at a critical stage of the development of an animal. If this were correct, autoantibodies could only be generated by somatic mutation with the development of a "forbidden clone" of lymphocytes.

Some evidence still supports this elegant hypothesis, but unfortunately it has proved far too simple, as numerous contradictory data have been collected; for example, B lymphocytes (the precursors of antibody-forming cells) that react to host antigens can regularly be found in the blood of normal animals—in other words, they have not been eliminated. Furthermore, tolerance to some foreign antigens can be induced in experimental animals by special immunization schedules and lymphocytes transferred from such animals can render normal animals tolerant to the same antigen. This suggests that tolerance is an active process somehow maintained by lymphocytes.

Since these experiments, numerous further studies have shown that collaboration between certain populations of T lymphocytes and B lymphocytes is required for antibody production, but that other populations of T lymphocyte (suppressor cells) are capable of abrogating the response.

Currently, it is believed that autoantibody production is the result of failure of these control systems. In some instances (SLE for example) failure seems to be general, so that many separate autoantibodies are produced; in others (like anti-GBM antibody-induced nephritis) failure seems to be unique to a single autoantibody. Either way the conclusion is encouraging, as it should be easier to regain control of an immune response than to eliminate "forbidden clones" of lymphocytes. Animal studies are already being directed towards this goal.

Initiating factors (Talal, 1977). Autoantibody production requires certain pre-conditions, in particular a genetically susceptible host and an initiating event. Genetic susceptibility is now known to be multifactorial, with the most important component associated with the tissue type, perhaps because genes that control it lie in the same region as immune response genes—these are genes that determine whether an animal can respond to an antigen or not. In all experimental models of autoimmunity studied so far, susceptibility is indexed by the tissue type, while the numerous associations between HLA (tissue type) antigens and autoimmune diseases suggest the same is true for man (Bodmer, 1978).

Tissue damage and infection are the two best studied events believed to initiate autoantibody production. Tissue antigens are released into the circulation after injury, which, in a susceptible host, may provoke autoantibody production. Infection probably acts in a variety of ways; some organisms are antigenically very similar to host tissues (molecular mimicry), for example similarity between some streptococci and myocardium. Other organisms such as mycobacteria and *B. pertussis* are adjuvants—that is they non-specifically enhance antibody responses and may, in some subjects, allow autoantibodies to escape suppression. Finally, some organisms directly invade and disorganize the immune system. Each of these effects has been established in experimental models of autoimmunity, but the implications for human disease remain speculative.

Mechanisms of injury (inflammation) (Weissman, 1975). In experimental models (Rose et al., 1977) as well as man (Rees, Lockwood and Peters, 1978) overt disease does not invariably accompany high titres of autoantibody. Damage depends on the inflammatory response which is a mechanism for amplifying injury. Numerous mediators are involved, some cellular and some humoral. Some humoral mediators, such as complement, coagulation and kallekrein systems, have been extensively studied and their relation to cellular mediators such as neutrophils and monocytes has been defined. Much less information is available about others such as C-reactive protein, orosmomucoid and haptoglobin, and their role is much less clear.

Cells are the most potent cause of injury. They are fixed at the site of antibody deposition by receptors which are present on their surface, for the Fc portion of antibody molecules. This also provides the stimulus for phagocytosis and for release of lysosomal enzymes. It is these enzymes which digest adjacent structures, be they bacteria, host tissue or other material. Relatively high concentrations of antibody must be fixed before cells can be engaged. However, the sensitivity of the system can be increased 10-fold or more by the presence of complement which also binds to antibody and provides a double stimulus for the neutrophils and monocytes, as they also have receptors for complement. Neutrophil- and monocyte-mediated injury is probably the most important mechanism of inflammation, but others involving K (killer) eosinophils, cells and the lytic reaction of complement also have a place. Details of these and other mediators of inflammation should be sought in those references which are general reviews.

Two important concepts emerge from the study of inflammation: first, the inflammatory potential of an animal can be greatly enhanced by adjuvants and infections and that inflammation may be initiated wherever antibodies—or, for that matter, immune complexes—are deposited. This suggests that intercurrent infection in a patient with autoimmune disease may, by increasing the inflammatory potential, induce exacerbation of the primary disease without change of autoantibody titre. In fact, just such a phenomenon has been described in Goodpasture's syndrome caused by antibodies to GBM (Rees, Lockwood and Peters, 1977).

Second, suppression of inflammation is the most important therapeutic manoeuvre in fulminant disease. This is probably why high-dose steroids and plasma exchange are the most effective treatments of acute disease.

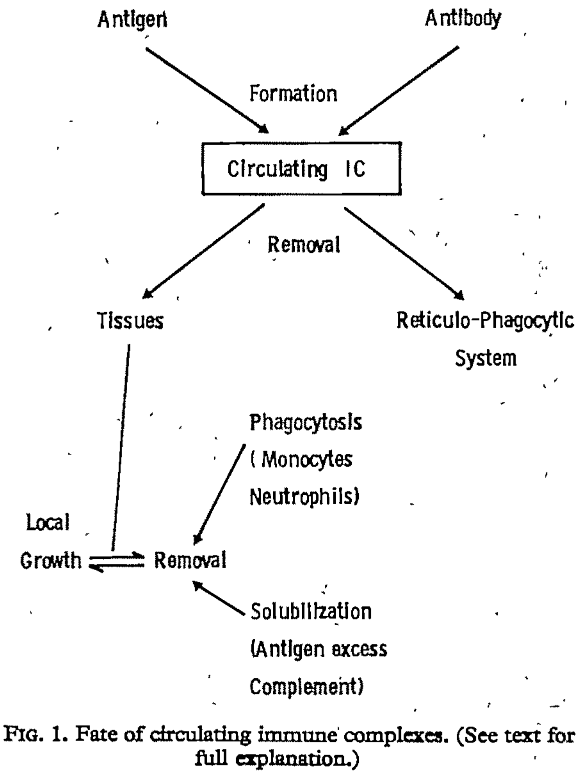

FIG. 1. Fate of circulating immune complexes. (See text for full explanation.)

Immune complexes (Cochrane and Koffler, 1973; Haagenstad and Mannik, 1977) (fig. 1).

Small amounts of immune complexes are formed continually and removed from the circulation by macrophages of the reticulophagocytic (reticuloendothelial) system. The efficiency with which they are cleared depends on certain properties of the complexes, such as size, antibody class and sublcass and the nature of the antigen. In particular, complex size seems to be important. Large complexes formed at high relative concentrations of antibody are cleared easily, whereas medium-sized complexes formed in slight antigen excess are poorly cleared and liable to deposit in tissues; very small complexes are neither cleared nor deposited. Thus medium-sized complexes are pathogenic.

The duration of complex deposition is also important, transient deposition causing transient disease whilst more prolonged deposition may be responsible for severe structural damage. In experimental animals most spontaneous immune-complex disease is caused by persistent, and often inapparent, viral infection; it is possible the same is true for man.

In the past few years much interest has been generated by the possibility that subtle forms of immune deficiency might increase susceptibility to chronic immune complex disease, since infections would be poorly eliminated (Soothill, 1975). Evidence for this derives from many sources, one of the most striking being the increased frequency of immune complex disease in patients with hereditary deficiencies of complement (Lachman and Hobart, 1978).

Thus, stratagems designed to stimulate the immune system might provide the basis of therapy for these diseases in the future—that is, provided, they did not also enhance inflammation.

CLINICAL ASPECTS OF AUTOIMMUNITY

Despite the uneasy nature of the transition when turning from experimental studies of autoimmunity to purely clinical matters, certain principles remain true. For instance, at least two fundamentally different mechanisms of injury are involved. Antibody-mediated damage—often referred to as type II reactions after the Gell and Coombs (1962) classification of hypersensitivity—shows specificity for a particular tissue and is not usually accompanied by signs of systemic inflammation, whereas immune complex deposition type III reactions (Gell and Coombs, 1962) affect many organs and are frequently accompanied by systemic inflammation.

Widespread inflammation is also characteristic of septicaemia which, not surprisingly, has many clinical features in common with fulminant immune complex disease. Both may be accompanied by fever, weakness, confusion, cardiorespiratory and renal failure. Drawing the distinction between them presents particular problems in intensive therapy units where clinicians are naturally reluctant to subject critically ill patients, whom they suspect have septicaemia, to invasive investigations such as renal biopsy and arteriography, which may be necessary before use of immuno-suppressive drugs and plasma exchange are considered. It cannot be emphasized too often that to leave a patient with fulminant glomerulonephritis untreated for 24 h may be to sacrifice all hope of regaining useful renal function. Fortunately, most patients do not present such immediate problems and therapy can convert the results of appropriate investigations (table II). Such investigations will now be discussed in the context of individual diseases.

TABLE II. *Investigations of autoimmunity*

Haematology	Hb, ESR, WCC and differential, platelets
Renal	Urine microscopy, urine protein estimation plasma urea and creatinine, serum proteins, I.V.U.
Respiratory	Chest x-ray, sputum culture, respiratory function tests, *k*CO
Immunological (general)	Immunoglobulins, complement
Specific	Acute antibodies, rheumatoid factor, Coombs test, tissue auto-antibodies, A.N.F.
Immune complexes	Cryoglobulins, immune complex assays
Biopsies	Of affected tissue, e.g. lung, kidney
Arteriography	

Antibody-mediated disease (Roitt, 1977).

Numerous autoantibodies have been detected, usually by indirect immunofluorescence (a technique in which test serum is incubated with normal tissue which is then washed and stained for immunoglobulin: the only immunoglobulins that remain on the tissue section are firmly bound antibody molecules), but the significance of many of them is uncertain. Some are specific to organs such as thyroid, pancreas and kidney, and these are generally thought to be pathogenic. Others are non-organ specific and react with mitochondria or nuclei of many tissues; these are probably not pathogenic (except perhaps in immune complexes), but may serve as markers of specific diseases.

Individual diseases will now be considered.

Endocrine disease (Volpe, 1977)

The thyroid is the commonest site of autoimmune disease. Three distinct syndromes are recognized: Graves' disease caused by an antibody (LATS—long acting thyroid stimulator) which mimics thyroid stimulating hormone (TSH); primary myxoedema, which is associated with antibodies to thyroid microsomes and to thyroglobulin; Hashimoto's disease, which is associated with these same antibodies but with greater inflammation in the gland. Autoimmunity in these patients rarely presents special problems for anaesthetists. It is of interest that they also have a greatly increased frequency of antibodies to other endocrine glands such as the pancreas, adrenal, pituitary, testis, ovary and stomach. This suggests a genetic susceptibility for this type of antibody, which is supported by the increased frequency of the tissue type HLA-B8, DW3, in these patients.

Haematological disorders (Dacie and Worlledge, 1975)

Haemolytic anaemia. Autoimmune haemolytic anaemia may arise *de novo*, following infection (especially mycoplasma pneumonia), or be one aspect of a systemic disease such as SLE. There may be a severe anaemia (the haemoglobin may decrease to 3–4 g dl^{-1}) and splenomegaly is common.

Laboratory findings reflect haemolysis. The direct antiglobulin (Coombs) test is positive and is used to confirm the diagnosis. Most commonly the autoantibodies are IgG, reacting optimally at 37 °C (warm antibodies) and are directed against Rhesus blood group antigens. Occasionally IgM antibodies are found, usually after mycoplasma pneumonia when antibodies fix best at temperatures below 37 °C (cold reactive antibodies). Nursing patients with cold antibodies in a warm atmosphere is an important aspect of management.

High-dose steroids (up to 60 mg prednisolone per day) are used for immediate treatment—refractory cases may benefit from splenectomy.

Thrombocytopenia. Immune damage to platelets may also be an isolated phenomenon or associated with systemic disease (SLE, lymphoma and some infections). Antibodies may be detected on platelets which have receptors for the Fc portion of antibody molecules. Sometimes antibodies can also be detected in serum. Platelet counts may decrease to less than

20 000 mm^{-3}. Treatment demands high-dose steroids, but a favourable response may be delayed for 2 weeks or more. Plasma exchange has occasionally been used.

Neutropenia. Very rarely, autoantibodies cause neutropenia.

Skin disease

The allergic basis of drug rashes is well established, as are rashes associated with immune complex disease such as SLE. More recently, autoantibodies have been described in life-threatening bullous disease.

Pemphigus vulgaris. Pemphigus affects the middle-aged. It is characterized by generalized flaccid blisters which show little tendency to heal. Before the advent of steroids, the disease was uniformly fatal and even now mortality is high. Diagnosis is clinical and confirmed by histology and immunofluorescent examination of the skin which shows IgG (autoantibody) deposits in the inter-cellular space.

Pemphigoid. Pemphigoid affects older patients and the bullae are more resiliant. Antibodies to skin basement membrane can be demonstrated in 80% of patients. High-dose steroids are the mainstay of therapy, but azathioprine and methotrexate have also been used.

An autoimmune basis of some less severe skin diseases such as herpes gestationes has also been demonstrated; standard texts should be consulted for details about them.

Renal disease

Antibody-mediated glomerulonephritis (Wilson and Dixon, 1973; Rees, Lockwood and Peters, 1978). Antibodies to glomerular basement membrane (GBM) are a rare but usually devastating cause of disease. Although subacute forms do occur, the nephritis is usually fulminant and renal function may be lost in a matter of hours (fig. 2). Examination of urine reveals an abnormal sediment and proteinuria, plasma urea and creatinine reflect renal function whilst renal biopsies show focal necrotizing glomerulonephritis with crescents. Immunofluorescent preparations reveal characteristic linear staining of the GBM with IgG. Anti-GBM antibodies also cross-react with alveolar basement membrane and about 90% of patients have pulmonary haemorrhage which may precipitate respiratory failure. Even severe pulmonary haemorrhage may not cause haemoptysis, in which case confirmation of the radiological diagnosis can be accomplished by measurement of uptake of carbon monoxide per unit volume of lung (*k*CO) which increases after pulmonary haemorrhage (Ewan et al., 1976). Pulmonary haemorrhage is exacerbated by fluid overload, so that great care must be taken when transfusion is used to correct severe anaemia, which is a feature of this disease.

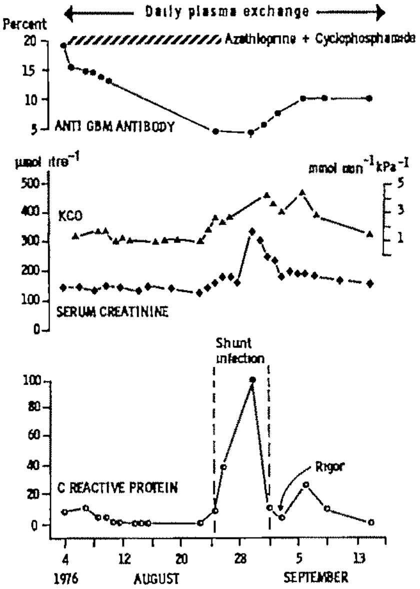

FIG 2. Record of an individual patient with Goodpasture's syndrome.

Muscle disease (Walton, 1977)

Myasthenia gravis is caused by an antibody to acetylcholine receptors on the post-synaptic membrane, which either blocks receptors or accelerates their degradation. Young women are most commonly affected and abnormalities of the thymus, either hyperplasia or adenoma, are found in 80% of patients. Cardinal symptoms are muscle weakness and fatiguability; the severity varies greatly and exacerbations follow intercurrent infection. Involvement of bulbar or respiratory muscles may lead to respiratory failure.

Clinical diagnosis is confirmed by the tensilon test. A favourable response to this short-acting anticholinesterase should be seen within minutes of i.v. injection. Laboratory investigations are usually normal, except for the presence of anti-receptor antibodies. Patients with IgA deficiency have been described occasionally.

Conventional treatment is with long-acting anticholinesterases, such as pyridostigmine. Improvement may follow thymectomy, even when the gland is histologically normal. High-dose steroids are a useful adjunct in refractory cases, but must be introduced gradually to avoid the risk of acute exacerbations. Recently, the benefits of plasma exchange and immunosuppressive drugs have been shown (Pinching, Peters and Newsome-Davies, 1977). They are discussed elsewhere in this issue (p. 21).

Immune complex disease

As alluded to above, immune complex (IC) disease is much more variable than that resulting from antibodies. This reflects the sites where complexes deposit; the joints, skin and kidney seem peculiarly vulnerable. Several distinct syndromes have been defined, these divisions are arbitrary but are retained for clinical convenience rather than from scientific merit.

Techniques for measuring IC in sera have recently been developed. There is as yet not one ideal assay and current assays detect different properties of the complexes. Consequently the proportion of "positive" patients with a particular disease depends on which assay is used (fig. 3). Despite this, results from some assays can be clearly correlated with intensity of disease activity (Pussell et al., 1978). However, it still has to be proved in human disease—as opposed to experimental analogues—that the complexes detected in the circulation are pathogenic. With this caveat, some individual diseases will now be considered.

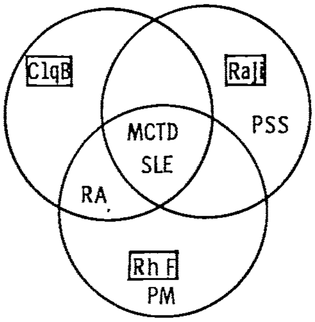

FIG. 3. Detection limitations of different IC assays in connective tissue disease. Positive immune complex assays within the circles C1q, Raji and RhF are three separate assays. RA = rheumatoid arthritis; SLE = systemic lupus erythematosis; PSS = scleroderma; MCTD = mixed connective tissue disease.

Systemic lupus erythematosis (Hughes, 1977) (table III). SLE is often regarded as the archetypal immune complex disease. Signs and symptoms are protean: skin, joints, kidney and central nervous sytem are prominently affected. Additional features result from autoantibodies to red cells, platelets, lymphocytes and cerebral tissue.

TABLE III. *Systemic lupus: cardinal features*

Clinical	Musculo-articular
	Cutaneous
	Fever
	Neuro-psychiatric
	Renal
	Pulmonary
	Haematological
Investigations	DNA binding increased
	Positive ANF
	LE cells
	Complement reduced
	Immune complexes present

Common presenting features are a photosensitive rash and arthralgia, but more severe disease, for example glomerulonephritis or cerebral disease, may be manifest from the outset. Pulmonary haemorrhage is an unusual but severe complication.

Investigation should include a full blood count and a thorough search for renal involvement, including microscopy of a fresh specimen of urine. Immunological tests reveal the hallmark of the disease—anti-DNA antibodies—and their detection has replaced LE cells as the arbiter of diagnosis. Anti-nuclear factor (ANF) is also positive, but less specific. Immune complexes are present in about 50% of patients. Low serum concentrations of complement (low C2, C4, C3) are almost invariable in active disease.

Treatment of mild disease is with simple anti-inflammatory drugs. More severe disease requires steroids, or sometimes immunosuppressive drugs and plasma exchange.

Rheumatoid arthritis (Bluestone and Bacon, 1977). Rheumatoid arthritis is a chronic deforming disease thought to be caused by immune complexes. Women are mainly affected and the frequency increases until the sixth decade. Initial symptoms are confined to joints, especially the hands, wrists, knees and hips. Subcutaneous nodules are pathognomic and are found in 20–25% of patients. Extra-articular manifestations are less common, but haemolytic anaemia caused by hypersplenism (Feltys Syndrome), lung disease with effusions, nodules and fibrosis, and systemic vasculitis may occur.

Rheumatoid factors—antibodies to immunoglobulins—are a hallmark of the disease, but are only positive in 60% of patients when tested by conventional means. Immune complexes are found in most patients, but complement concentrations are normal. Treatment is with simple anti-inflammatory drugs and steroids are used only when vasculitis is present.

Polyarteritis nodosa (*PAN*) (Rose and Spencer, 1957) (table IV). PAN is characterized by widespread vasculitis that may affect any organ. In some parts of the world it is associated with chronic carriage of hepatitis B antigen, but this does not seem to be true in the U.K.

TABLE IV. *Polyarteritis: cardinal features*

Clinical	Fever Rash Glomerulonephritis Hypertension Acute abdomen Neuropathy (mononeuritis multiplex) Pulmonary haemorrhage
Investigations	Leucocytosis Hyperglobulinaemia Rheumatoid factor Biopsy: vasculitis, glomerulonephritis Arteriography: aneurisms.

Typical presenting symptoms are fever, arthralgia, myopathy and weight loss with progression to include peripheral neuropathy, pulmonary vasculitis and renal disease. Severe hypertension and abdominal pain are prominent in those with involvement of medium-sized vessels, whilst a necrotizing glomerulonephritis is found in those in whom smaller vessels are affected.

There are no pathognomic laboratory tests. Neutrophilia and eosinophilia are common; urinary investigations provide evidence of nephritis. Immunological investigations are similarly non-specific and results of muscle biopsies are usually equivocal. Renal biopsies reveal the nephritis, but when severe hypertension is present, visceral arteriography is the most important investigation. It may reveal multiple aneurysms and should be regarded as an emergency. Treatment is discussed elsewhere in the issue (Pinching, p. 21).

Wegener's granulomatosis (Fauci and Wolff, 1973). Wegener's should probably be regarded as a variant of the microscopic form of PAN. Most of the clinical features are identical, but in addition granulomata in the upper respiratory tract and lungs cause local symptoms. There are no pathognomonic immunological features; the treatment is discussed by Pinching (p. 21).

Other vasculitides. Henoch–Schönlein purpura (Meadow et al., 1972) predominantly affects children; and is characterized by arthritis vasculitis and glomerulonephritis. The rash is characteristic. There are no special serological features, but IgA deposited in kidney and skin offers a useful confirmation of diagnosis.

Mixed cryoglobulinaemia (Brouet et al., 1974) affects the elderly. Cryoglobulins (proteins that precipitate in the cold) are found in serum and are associated with severe cutaneous vasculitis and some times glomerulonephritis. Plasma exchange may be beneficial.

Diseases of unknown aetiology

Scleroderma (systemic sclerosis) (Cannon et al., 1974). This disease chiefly affects women and is characterized by diffuse sclerosis of the skin, gastrointestinal tract, heart and lungs. Raynaud's phenomenon is found in 80% of patients. The sudden development of accelerated hypertension and irreversible renal failure is the commonest cause of death. Treatment is unsatisfactory, but recently isolated reports suggest that vigorous control of the hypertension may allow the kidneys to recover in some patients.

Polymyositis and dermatomyositis (Pearson, 1974). This disease is characterized by progressive muscle weakness that may be accompanied by a rash; proximal muscles are particularly severely affected but pharyngeal and respiratory muscles may also be involved. Careful monitoring of respiratory function (for example vital capacity) is mandatory. Forty per cent of patients have skin changes which are frequently diagnostic. They consist of a purplish rash on the upper eyelids which is associated with periorbital oedema. Development of the disease is frequently associated with an occult neoplasm. Investigations show increased concentrations of muscle enzymes (c.p.k., s.g.o.t. and aldolase); e.m.g. and muscle biopsy may also be diagnostic. Treatment is unsatisfactory and involves large doses of steroids; plasma exchange does not seem to be beneficial.

CONCLUSIONS

Experimental studies have provided clear, although as yet incomplete, ideas of the basis of autoimmunity and have identified novel approaches to therapy such as plasma exchange combined with immunosuppressive drugs. Unfortunately, despite this, numerous immediate clinical problems remain, especially in the management of life-threatening disease. One of the most pressing of these is to distinguish between infection and fulminant immune complex disease (table V). This difficulty is made worse by two factors; first, treatment of severe autoimmune disease almost invariably involves steroids or immunosuppressive drugs which increase susceptibility to infection, and second, infection itself can exacerbrate the underlying disease. The choice is often between more immunosuppression, or less. Under these circumstances early invasive investigations, especially with regard to possible chest infections require early bronchoscopy and lung biopsy, which should be mandatory where uncertainty exists. Currently there are few reliable indices of disease activity and many judgements need to be purely clinical.

TABLE V. *Autoimmune disease: aims in the critically ill*

(1) Distinguish disease activity from infection
(2) Establish definite diagnosis
(3) Start specific therapy

Finally, it must be stressed that, without excellent basic medical care of cardiorespiratory and other systems, attention to asceptic techniques and good nursing, complex and potentially dangerous modern approaches to therapy are little more than an extravagant waste of time.

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RECENT ADVANCES IN IMMUNOLOGICAL THERAPY: PLASMA-EXCHANGE AND IMMUNOSUPPRESSION

A. J. Pinching

The specialty of clinical immunology can be seen to involve virtually every clinical discipline; many diseases not apparently of immunological nature may have some immunological facet. While some physicians may resent the intrusion of immunology into so many areas, it represents no more than the formalization and considerable extension of the concept of host factors in disease and disease susceptibility. Any attempt to review therapy in immune disorders from such a viewpoint would necessarily be too broad. Therefore it seems more appropriate to take a specific growing point, which, apart from its direct applicability, can serve to illuminate many related aspects of the immunological approach to treatment. The topic chosen is that of immunosuppression and plasma-exchange in autoallergic disease. This growing point involves a relatively novel approach in therapy that urgently needs a perspective. The fact that it is often used in patients with fulminating diseases, sometimes affecting multiple body systems, makes it a particularly appropriate topic for anaesthetists.

In recent years, a variety of disorders have been treated with plasma-exchange regimes and some striking results have been obtained. In particular, the treatment and understanding of antibody-mediated diseases such as fulminating lung haemorrhage and rapidly progressive nephritis (Goodpasture's syndrome) (Lockwood et al., 1976, 1977b) and the more chronic, but disabling, myasthenia gravis (Pinching, Peters and Newsom-Davis, 1976; Dau et al., 1977; Newsom-Davis, Pinching et al., 1978; Newsom-Davis, Ward et al., 1978) have been radically altered by the use of such regimes. Immune-complex diseases, where circulating or tissue-bound complexes are thought to be of major pathogenetic importance, have also shown striking response to regimes including plasma-exchange; for example rapidly progressive nephritis (Lockwood et al., 1977a, b), often associated with systemic disease such as polyarteritis or Wegener's granulomatosis, some cases of systemic lupus erythematosus (Verrier-Jones et al., 1976; Lockwood et al., 1977b; Moran et al., 1977) and cutaneous vasculitis. It seems appropriate, therefore, to consider the mechanisms whereby these regimes influence tissue damage in disease and to review their impact on the management of such patients.

The technique: vascular access

During plasma-exchange the patient's plasma is separated from the cellular elements of blood and the latter are returned to the patient with a plasma solution, such as plasma protein fraction (PPF); strictly speaking, the term plasmapheresis (which is widely used interchangeably with plasma-exchange) refers to the exchange of plasma for crystalloid solutions. The procedure has been greatly simplified in recent years by the use of cell separators, which may be readily adapted for plasma-exchange; they enable rapid exchange and avoid many of the laborious aspects of hand-pack exchange. Blood is taken from the patient, is anticoagulated and passes into a centrifugation chamber. Here, plasma is separated from the cellular elements and can be "creamed off". The cells are returned to the patient with plasma substitute, the latter being matched in volume for the plasma removed. Two basic designs exist for these machines, which differ in that one has a continuous and one a semicontinuous flow system. The advantages and disadvantages of the two systems are beyond the scope of this review.

Plasma-exchange may be performed via venepuncture of large veins or, for frequent repeated exchanges, via arteriovenous shunt or fistula, as used for haemodialysis. The choice depends upon the nature of the disease, the possibility of renal failure in the long term and the likely duration and frequency of exchanges.

Plasma solutions used

The two plasma fractions most commonly used to replace that removed are plasma protein fraction

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(PPF) and fresh-frozen plasma (FFP). While the former is highly purified fraction (Cohn fraction 5) consisting largely of albumin and minerals, the latter also contains many of the active plasma globulins. The manipulation of the patient's plasma environment will be very different, depending on the type of plasma used and this will vary according to the clinical situation (Moran et al., 1977). By using PPF, the patient is depleted of globulins, notably immunoglobulins, coagulation factors and many of the acute phase proteins (Lockwood, Pussell and Peters, 1978), quite apart from the removal of abnormal substances in the plasma such as autoantibodies or immune complexes. The use of FFP, on the other hand, will largely restore globulins so that the manoeuvre is more restricted to the removal of abnormal or excess plasma constituents. In addition, in certain diseases the use of FFP may actually enrich the patient's plasma with certain factors (e.g. complement in SLE). Availability of plasma may determine what solution is used; and in certain situations, FFP is used at the end of exchange to minimize the enhanced risk of bleeding as a result of depletion of fibrinogen and other clotting factors.

The effect of plasma-exchange on various plasma factors

The sequential nature of the exchange means that, during the time taken for the procedure, the law of diminishing returns applies to the removal of plasma factors. It has been shown by marker techniques that, after a 2-litre exchange, 75% of an intravascular marker is removed and after 4 litre, 95% is removed (Lockwood, Pussell and Peters, 1978). Many of the substances being removed, however, are distributed between the intravascular and extravascular spaces (e.g. immunoglobulins); the ratio of this distribution and the rate of equilibration between these spaces of particular substances will determine the net effect of plasma-exchange on total body concentrations and thus the extent of the increase in plasma concentrations immediately after exchange. The major factor in the short-term effect of plasma-exchange is the frequency of exchanges. This should be planned from knowledge of the rates of equilibration between body compartments. For immunoglobulins, the half-time for equilibration between intravascular and extravascular compartments is 1–2 days; therefore, to achieve adequate depletion of an immunoglobulin, exchanges should be carried out daily for the initial period of treatment. The rate of synthesis of plasma factors will clearly be the most important determinant of the longer-term effect of exchange and its duration of action; it may be that the exchange itself could influence the rate of synthesis.

In exchanges for PPF, there is moderate defibrinogenation and decrease in other clotting factors, but in the absence of major bleeding points or the use of anticoagulants, this rarely causes clinical problems (the amount of heparin returned to the patient during the procedure is minimal). Complement components are also reduced (Lockwood, Pussell and Peters, 1978) along with other active plasma proteins, but return to normal concentrations relatively rapidly after the end of a series of exchanges, as would be expected from their high synthetic rate. It is clear that reductions in coagulation factors, complement components, kinins and other acute-phase proteins will be of importance in reducing the inflammatory response and, presumably therefore, the tissue damage resulting from it; however, it seems that the safety factor for the normal biological activity of these proteins means that relatively few adverse effects are seen from their reduction.

Total immunoglobulin concentrations are similarly reduced by plasma-exchange and the time course of their return may be substantially delayed by immunosuppression; the concentrations of specific autoantibodies will also be strikingly reduced and immunosuppression may delay their reappearance to a greater extent than that for total immunoglobulin (see below).

Immune complexes are of varying pathogenicity, depending among other things upon size, determined in turn by antigen–antibody ratio; this will determine the handling and tissue damaging potential of such complexes. Plasma-exchange itself, apart from actually removing formed complexes (Lockwood et al., 1977a; Pussell et al., 1978), could alter the ratio of antigen to antibody: while the depletion of both would be similar, their rate of generation is likely to be different. The physical removal of circulating complexes could also restore the capacity of the reticuloendothelial system to clear further immune complexes, as it is thought that the presence of such circulating complexes represents in part the blockade of the RES by an excess of complexes.

Much of the foregoing has underlined the fact that the value of plasma-exchange in treating autoallergic disease is largely dependent upon interfering with generation of the immunopathogenetic factor by other means. Exchange allows the disease to be controlled relatively rapidly while this longer-term control is established.

Immunosuppression and corticosteroids

Immunosuppressive drugs may act by reducing the synthesis of autoantibodies by a cytotoxic effect on dividing B lymphocytes or plasma cells, or possibly by alterations in T cells of the helper type. Cyclophosphamide and azathioprine are the drugs most widely used in this situation. It is known from animal studies that the removal of antibody during the phase of active antibody synthesis (after immunization) will lead to feedback stimulation of antibody production (Bystryn, Schenken and Uhr, 1971). As this is likely to involve generation of new cells, this feedback could actually enhance the effect of cytotoxic agents so that plasma-exchange, when combined with immunosuppression, would lead to a "suicidal proliferation" of the clone of cells responsible. On the other hand, there are recent suggestions that the continuing synthesis of autoantibody may be dependent upon circulating concentrations of antibody (Hall et al., 1977); its removal might switch off the clone.

It is possible that the control of immune complex disease by immunosuppressive or steroid drugs, or both, may depend upon their capacity to alter the antigen–antibody ratio, presumably by reducing antibody formation. This could either improve the capacity of the RES to handle the complexes or decrease their tissue-damaging effects, or both. As these alterations may take some time to develop, as in autoantibody-mediated disease, a period of plasma-exchange may tide the patient over until they are established. It is perhaps appropriate to note at this stage, that immune complex disease is thought to represent relative immunodeficiency (Peters and Lachmann, 1974; Soothill, 1974), as an adequate antibody response would enable rapid elimination of antigen. On the other hand, complete lack of antibody response will prevent toxic immune complexes from being formed. In the absence of an effective immunostimulant to antibody production, the less satisfactory option of further immunosuppression of a host already presumed to be immunodeficient has to be used.

Corticosteroid drugs are frequently combined with plasma-exchange. Surprisingly little is understood of their particular role, but it seems likely that they are beneficial in two major respects. First, their powerful anti-inflammatory effect may minimize the tissue damage caused by the antibody or complexes already deposited; this may also be a significant part of the role of immunosuppressive drugs. Second, high-dose steroids exert an effect on populations of T and B lymphocytes (Weston, Claman and Krueger, 1973; Fauci and Dale, 1974; Yu et al., 1974); this appears to be by altering the proportions in different sites or pools and this may underlie an immunosuppressive effect not dependent upon cell division. There is, however, no evidence that high-dose steroids are lympholytic (or specifically destructive of lymphocytes) in man, although this effect is seen in some species (Weston, Claman and Krueger, 1973).

While the combination of plasma-exchange and immunosuppression and steroids is inevitably regarded from the viewpoint of humoral effects, it is likely that the suppression of the polymorph and platelet lines by cytotoxic drugs is of importance in the reduction of inflammatory injury mediated by these formed elements of blood. Furthermore, steroids undoubtedly have effects on macrophage (Rinehart et al., 1974) and neutrophil function which may also limit the damage caused when these cells interact non-specifically or via specific receptors for immunoglobulin or complement (Schreiber et al., 1975) with tissue-fixed antibody or immune complexes.

Hazards of plasma-exchange regimes

There are relatively few specific hazards of plasma-exchange itself. Indeed, most of the problems associated with our experience of the procedure have involved arteriovenous access sites needed for prolonged periods of exchange. These sites (shunts in particular, but also fistulae) are a potential site for serious infection, especially in patients receiving immunosuppressive therapy, and are a potent cause of morbidity. The procedure itself takes 1.5–2 h and the patient lies comfortably on a bed or couch; occasionally paraesthesiae, cramps or abdominal or back pain are encountered, and painful venous spasm is sometimes seen when blood is given. When the semi-continuous method is used the patient may develop symptoms of anaemia such as angina or syncope if the exchange is performed with a starting haemoglobin less than 8 g litre^{-1}, and it is normal practice to correct this before or at the onset of the exchange. PPF, being a highly purified bland albumin solution, has few side-effects, while FFP carries the risk of febrile reactions, urticaria, etc., and the small risk (in the U.K.) of transmitting Hepatitis B. Hypoalbuminaemic patients, particularly those with renal impairment, may require some reduction in the amount of plasma given to avoid too rapid an increase in serum albumin during the first days of exchange, as fluid retention and hypertension may otherwise develop.

Bleeding from visceral biopsy sites, from peptic ulcer or other potential bleeding points is an occasional and significant hazard secondary to the defibrinogenation seen following plasma-exchange for PPF. This risk of bleeding may to some extent be obviated by the use of FFP (2–3 units) as the exchange solution at the end of procedures performed on patients at risk. The slight decrease in platelet count occurring during the exchange is rarely of clinical significance except in severely thrombocytopenic patients in whom platelet transfusion may be needed.

Increased susceptibility to infection is a well-recognized feature of immunosuppression and high-dose steroids, particularly when the patients become neutropenic. Plasma-exchange alone seems to have little, if any, effect of this sort, but it is not yet clear if it adds to the risks of immunosuppressives and steroids alone. Apart from infection of access sites with Gram-positive organisms, the infections seen with combined regimes tend to be with Gram-negative organisms or with opportunists such as *Pneumocystis carinii*, Candida, Aspergillus, *Herpes simplex* and Cytomegalovirus. The type of infections seen in hypogammaglobulinaemic patients (e.g. pneumococcal) are not particularly frequent after plasma-exchange.

Attention has been drawn to the effect of plasma-exchange on plasma cholinesterase (Woods, 1977). Although the observations on cholinesterase concentrations are not in question, their clinical significance has yet to be established, as the index case in the study referred to suffered respiratory failure for other reasons and had not had significant plasma-exchange at the time this developed (Pinching and Rees, 1977). The relevance of these observations to the beneficial effect of plasma-exchange in myasthenia gravis is also very doubtful.

Anti-GBM disease

The first major application of plasma-exchange in autoallergic disease was in Goodpasture's syndrome caused by antiglomerular basement membrane antibody (anti-GBM AB) (Lockwood et al., 1976). In this syndrome a high mortality from fulminating lung haemorrhage or rapidly progressive nephritis was previously seen; this was, curiously, combined with a much better comprehension of immunopathogenesis than for many other forms of nephritis. The term "anti-GBM disease" is now usefully employed to specify that the syndrome of lung bleeding and nephritis is indeed mediated by specific antibody, as similar pulmonary and renal manifestations may be seen (among others) in immune-complex-mediated disease. The spectrum of disease caused by these antibodies, which react with renal glomerular and lung alveolar basement membrane, is quite varied: either pulmonary haemorrhage or rapidly progressive nephritis may dominate the picture, while some patients have severe disease affecting both organs. The important clinical aspects are that renal function may be lost very rapidly (within days or weeks), although more indolent forms of the disease are seen; similarly, lung haemorrhage may be minor or life-threatening; in severe cases the very rapid loss of blood into the pulmonary alveoli and interstitium leads to extreme hypoxia which may prove difficult to reverse with artificial ventilation and high end-expiratory pressures. Death from lung bleeding was seen in about half the reported cases before the mid 1970's; the remainder usually either died from, or needed support for, end-stage renal failure. Treatment regimes with steroids, immunosuppressives and anticoagulants were generally ineffective and bilateral nephrectomy, which was at one time widely practised, was of doubtful efficacy and even more dubious theoretical rationale.

It seemed logical to try to remove the autoantibody by plasma-exchange to minimize the immediate tissue damage and to allow time for the control of further antibody synthesis by immunosuppressives (usually using cyclophosphamide 3 mg kg^{-1} day^{-1}, azathioprine 1 mg kg^{-1} day^{-1} and prednisolone 60 mg daily). Early successes were followed by an extensive experience in this rather rare disease (30 patients), enabling clarification of the role of such treatment (Lockwood et al., 1977b). In patients with significant residual renal function at the start of treatment, this function could in general be maintained and improved upon. Anuric patients and those with minimal renal function at the introduction of treatment did not show any improvement. Episodes of pulmonary haemorrhage were always controlled by a plasma-exchange regimen in the absence of specific exacerbating factors (infection, fluid overload); this included several patients estimated to be losing 600–750 ml of blood per day into their lungs, some requiring assisted ventilation. Plasma-exchange regimes should always be used in patients with active anti-GBM disease with pulmonary haemorrhage or nephritis, or both; patients without lung bleeding in whom all renal function has been lost do not benefit from treatment, but should be carefully observed for evidence of lung disease.

Infection-enhanced injury

During the course of these studies it was recognized that infection could exacerbate or initiate quiescent disease without any alteration in the concentrations of circulating autoantibody (Rees, Lockwood and Peters, 1977). This was attributed to the increase in non-specific inflammatory mediators provoked by infection which could enhance the damaging effect of a given amount of circulating or fixed antibody. It was this, among other things, that led to the recognition that plasma-exchange (for PPF) was not only removing pathogenetic antibody but also depleting many of the humoral mediators of the inflammatory response (coagulation factors, complement components, kinins and other acute-phase proteins). It is probable that part of the initial benefit of plasma-exchange is caused by such an anti-inflammatory effect. A further consequence was the realization that the widespread and immediate depletion of inflammatory mediators could be harnessed for the control of other conditions (e.g. immune complex disease).

Myasthenia gravis

A rather different opportunity for the study of the role of plasma-exchange in disease was in myasthenia gravis, in which the characteristic weakness and fatiguability is now recognized as being the result of a post-synaptic defect of the neuromuscular junction (Drachman, 1978). Recent evidence indicated that an autoantibody to acetylcholine receptor found in most patients with myasthenia is responsible for interfering with acetylcholine reception (Lindstrom et al., 1976); it may cause this by an allosteric effect on the acetylcholine binding site exerted from the antibody-binding site. Structural damage to the end-plate could also be antibody-mediated. There was, however, little firm evidence that the antibody was of pathogenetic significance in man. Quite apart from its potential therapeutic application, plasma-exchange offered the opportunity of studying two items of scientific interest. First, that the removal of antibody could result in clinically evident improvement, confirming a pathogenetic role for antibody as a "blocking factor" in transmission. Second, in the event of a clinical response myasthenia, by virtue of its chronicity, allows investigation of the effect of plasma-exchange alone. This is despite the fact that long-term immunosuppression for the control of antibody synthesis is a logical part of plasma-exchange regimes in this as in anti-GBM disease. Clear benefit from plasma-exchange was indeed seen in patients with acquired myasthenia gravis with circulating antibodies to receptor in our own studies (Pinching, Peters and Newsom-Davis, 1976; Newsom-Davis, Pinching et al., 1978; Newsom-Davis, Ward et al., 1978) and these observations have subsequently been confirmed by others (Dau et al., 1977). It was of particular interest that a patient with the clinically similar congenital myasthenia, in which antibodies are not found, did not improve with plasma-exchange (Pinching, Peters and Newsom-Davis, 1976). Furthermore, the second scientific point was well fulfilled, so that the efficacy of antibody removal alone has been established in this disease; it has also enabled controlled trials of the comparative efficacy of different immunosuppressive regimes with and without plasma-exchange to be conducted prospectively (Newsom-Davis, Ward et al., 1978).

It is clear that some myasthenic patients are not in a phase of active antibody synthesis and therefore may not require immunosuppressive treatment. Studies are in progress to try to determine which patients may benefit from plasma-exchange regimes. The obvious category for consideration is myasthenic crisis, including those with a fulminating course at presentation. Preparation for thymectomy in patients with limited respiratory reserve as a result of their disease would seem logical, as the morbidity of the procedure is in part dependent upon this function. Cholinergic crisis might also be treatable by plasma-exchange as the highly protein-bound anticholinesterases would be removed by the procedure. Patients with long-standing myasthenia, but who still have circulating antibody, in whom conventional measures are inadequate to control disease, are another potential group.

A recent study comparing different immunosuppressive regimes after plasma-exchange in myasthenia shows that the combination of cyclophosphamide 3 mg kg^{-1} day^{-1} and azathioprine 1 mg kg^{-1} day^{-1} may delay the reappearance of antibody to the greatest extent (Newsom-Davis, Ward et al., 1978), but only a few patients were in this group compared with those in cyclophosphamide or azathioprine alone groups. This interesting observation requires further study, and obviously has far-reaching implications for immunosuppressive regimes in other diseases.

In the light of this recent evidence on pathogenesis, an interesting clinical observation on patients with myasthenia may have wider implications. High-dose steroids (e.g. prednisolone 60 mg daily) are associated with an early (peak at *c.* 5 days) deterioration in the myasthenic state of such patients, and may even necessitate a period of assisted ventilation. Over the longer term they improve, although some may require unacceptably high doses to maintain the improvement. Whether the deterioration is the result of transiently increased tissue concentrations of antibody, increased fixation of antibody to acetylcholine receptor or enhanced activity of that already bound to the end-plate is unclear; it seems likely, however, that immunological alterations are responsible as specific neuromuscular effects of corticosteroids are not recognized. Such an adverse early effect of steroids would only be detectable in a disease such as myasthenia where day-to-day variation in the tissue effects of antibody may be closely monitored; if such an effect were to occur in other antibody-mediated diseases, with the possibility of increasing the tissue damaging effects of antibody, there would be important clinical implications. In myasthenia this effect can be avoided by the gradual increase of steroid dosage (Drachman, 1978), and this could be appropriate in other conditions.

Other autoantibody-mediated diseases

A number of other autoantibody-mediated diseases have been treated by immunosuppressive treatment and plasma-exchange regimes; similar insight has been gained by the investigational role of plasma-exchange as well as therapeutic benefits in *Herpes gestationis* (Carruthers and Ewins, 1978), idiopathic thrombocytopenic purpura (to control bleeding) (Branda et al., 1978) and in autoimmune B-cell deficiency leading to acquired hypogammaglobulinaemia (Tursz et al., 1977).

Immune complex diseases

In immune complex disease, the use of plasma-exchange to remove circulating immune complexes seems logical in those diseases in which the complexes are known or believed to have a pathogenetic role, for example rapidly progressive nephritis not caused by anti-GBM antibody, systemic lupus erythematosus and other vasculitides (Lockwood et al., 1977a, b; Pussell et al., 1978). The removal of complexes from the circulation by exchange may also enable the reticuloendothelial system to recover its capacity for removing further circulating complexes—a function which appears to be blocked by high concentrations of complexes (alternatively, the high concentrations reflect the incapacity of the RES). Furthermore, these immune complex diseases are frequently associated with a marked acute-phase reaction and the removal of the humoral mediators of inflammation is again likely to have a significant beneficial effect. In a few cases of chronic cutaneous vasculitis, it has been possible to document an immediate clinical effect of plasma-exchange alone which may last for some weeks or months, and is associated with the clearance of circulating immune complexes in the single patient in whom they are reliably detectable. Relapse in this case is preceded by reappearance of complexes.

Rapidly progressive glomerulonephritis

In most cases of immune complex disease the course of the disease prevents the study of plasma-exchange alone. In rapidly progressive nephritis, often appearing in the context of polyarteritis nodosa or Wegener's granulomatosis, the patients may show rapid loss of renal function as a result of crescentic glomerulonephritis (Lockwood et al., 1977a). Histologically, the appearances may resemble those seen in anti-GBM disease, but the immunofluorescence findings suggest immune complex deposition. These cases have, in general, been treated with combinations of steroids, immunosuppression and plasma-exchange, as used in anti-GBM disease. The response has been striking in many cases, with recovery of renal function even in patients with severe degrees of renal failure, including anuria; the extent of recovery seen is in general much better and more rapid than that seen in patients with anti-GBM of comparable severity. Other aspects of their systemic disease such as myopathy, hepatic disease, pulmonary vasculitis or granulomata, ocular disease and neuropathy may also show striking clinical response. Similar response may, however, be seen in patients with steroids and immunosuppression, without plasma-exchange; our evidence tends to suggest that plasma-exchange provides a greater rate of improvement and may possibly lead to a greater degree of improvement in terms of the final level of renal function achieved. However, a controlled trial is now in progress to try to establish whether or not plasma-exchange confers additional benefits. The disappearance of immune complexes from the circulation has been demonstrated in many of these patients, paralleling their clinical response (Pussell et al., 1978).

Systemic lupus erythematosus

In systemic lupus erythematosus, plasma-exchange has been used with apparently beneficial effect in individual patients in whom conventional treatment appeared to be ineffective in controlling disease, or in severe fulminating disease in which plasma-exchange was added to conventional agents from the outset (Verrier-Jones et al., 1976; Lockwood et al., 1977b;

Moran et al., 1977). However, the tendency of the disease to spontaneous variation or alterations in disease activity, provoked by the relatively frequent infections from which such patients suffer, makes assessment of the specific effects of plasma-exchange difficult. Similarly, the response to steroids, which are notably effective in this disease, may be delayed. For this reason the precise role of plasma-exchange in SLE is unclear, despite the obvious rationale for its use in what is clearly recognized to be an immune complex disease. The concentrations of circulating immune complexes can certainly be reduced by plasma-exchange and the effect may in some cases be sustained. Particular evidence of clinical response has been seen in patients with renal failure from severe diffuse proliferative lupus nephritis, in cerebral lupus and in the rare pulmonary vasculitis of lupus. However, it is not yet possible to define the role of plasma-exchange in lupus, other than in the treatment of extremely severe and often atypical cases. The use of immunosuppressive agents, although fairly widespread, has been less clearly of benefit than might be expected and the risks seem to be greater than in other diseases. This may reflect the fact that patients with lupus are already notably susceptible to infection, this probably being an indication of the underlying immunodeficiency that may lead to immune complex disease. It is perhaps appropriate to note at this stage that a significant number of patients with pulmonary complications of lupus, referred for the possibility of plasma-exchange, proved to have pulmonary infections, often of an opportunist type (such as cytomegalovirus and pneumocystis pneumonia); these must clearly be distinguished from active disease if possible, as the correct management is generally to reduce therapy rather than to escalate it.

Conclusions

The use of plasma-exchange and immunosuppression in autoantibody- or immune-complex-mediated disease started as an empirical approach to the treatment of a rare and fulminating disease; it has now been extended into widely differing specialties, not only as a therapeutic measure but also as a means for investigating disease pathogenesis. It has shed light on mechanisms of immunological injury and has enabled some analysis of the different roles of various therapeutic agents. A plasma-exchange regime is certainly not a universal panacea in immunologically mediated disease, but it represents a tool which, if used in carefully defined situations, can make an important contribution to therapy; its use necessitates careful monitoring of target organ damage and, where possible, of the mediators of disease.

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TUMOUR AND TRANSPLANTATION IMMUNOLOGY

J. E. Castro

Interest in the immune response developed from a study of the host's reaction to infection. Today the ramifications of immunology permeate a much broader span of medical practice. It is realized that selective suppression of the immune response may hold the key to the successful transplantation of tissues. In contrast, stimulation of the immune response may provide a means by which we can effect the rejection of cancers. This relationship between transplantation and tumour immunology is an important one and is the reason for inclusion of these two topics in this article.

Terminology

The immune response is the reaction of an individual to a substance or an organism which is foreign to it. The basic premise of tumour and transplantation immunology is that both grafts and tumours contain antigens foreign to the host. A clear understanding of the terminology that applies to tissue grafts is germane to both tumour and transplantation immunology:

A *syngeneic graft* is a graft exchanged between individuals of identical genetic constitution: for example, grafts between identical twins or mice of the same pure line strain.

An *allogeneic graft* is a graft exchanged between members of the same species but of different genetic constitution: for example, from one human to another or from one pure line strain of mice to a different one.

A *xenogeneic graft* is a graft exchanged between individuals of different species: for example, from monkey to man or mouse to elephant.

Tumour antigens

For a tumour to stimulate an immunological response it must possess characteristic antigens. Much of the early work on tumour antigenicity was confused because of the failure to appreciate the fact that tumours, like most other tissues, exhibit transplantation antigens. Only when syngeneic tumours are studied can consideration be given to those antigens that are characteristic of tumours. In animals this was possible after introduction of inbred mouse strains. Tumour-specific antigens are demonstrated experimentally when pretreatment with a syngeneic tumour influences growth if there is a subsequent challenge with the same tumour. Pretreatment may involve ligation or excision of the initial tumour after it has reached a critical size, but before dissemination (Klein et al., 1960), injection of a low dose of cells which is too low to induce an overt tumour, or injection of tumour cells that have been treated chemically or physically to prevent growth or division. If pretreatment alters the growth of an inoculation of tumour cells that would normally initiate an overt tumour in a non-treated recipient, then such pretreatment has caused an immune response to the characteristic antigens of the tumour. If pretreatment alters the growth of a tumour which is different from the one used for pretreatment, then cross-reactivity between the tumours used for pretreatment and challenge is said to occur. There are also *in vitro* techniques for detection of tumour antigens. Some involve the demonstration of tumour antibodies by membrane immunofluorescence, complement fixation or cytotoxicity, whilst others demonstrate lymphocyte cytotoxicity. Although antibodies to tumour antigens have been demonstrated by a variety of techniques, their significance *in vivo* is poorly understood.

It would appear that tumours may contain several antigens capable of stimulating an immune response: transplantation antigens, tumour-specific antigens, viral antigens, fetal antigens. Transplantation antigens are found on all tissues in vertebrates. Whether tumour-specific antigens are dependent upon new genetic information or whether they represent a derepressed fetal gene has yet to be established. Viral and fetal antigens are usually cross-reacting. The antigens induced by both DNA and RNA viruses are the same for all tumours induced by a single virus,

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irrespective of histological type, but differ from those induced by a different virus. The relationship between fetal and tumour antigens has been examined in a variety of ways (Stonehill and Bendich, 1970). Immunofluorescence studies have demonstrated fetal antigens on the surface of chemically induced tumours. Cytotoxic tests *in vitro* have demonstrated that lymphocytes from tumour bearers are sensitized against fetal antigens. *In vivo* most workers have found that pretreatment with fetal tissues protects against subsequent tumour challenge (Coggin, Ambrose and Anderson, 1971), but some have found that tumour growth is enhanced, and others have not found significant effects.

Demonstration of human tumour antigens depends upon *in vitro* techniques. Generally, human tumours contain common antigens shared by most, if not all, tumours of the same histological type. Cross-reactivity between tumours of different histological types is not usually found. This antigenic specificity is similar to that found in experimental tumours and it is evidence suggestive of a viral aetiology of most human tumours.

Immunosurveillance

The mechanisms whereby the host mounts a response against the antigens expressed by a tumour are known as immunosurveillance. It was stated by Burnet (1970) thus, "A major function of the immunological mechanism is to recognise and eliminate foreign patterns of behaviour arising in the body by somatic limitation or some equivalent process." This concept suggests that a mutant cell, which is potentially responsible for overt tumour development, has at least one antigen with a biochemical sequence different from that normally found in the host. An immunological response is, therefore, mounted against this antigen and may lead to the appearance of a clone of immunologically competent cells which eliminate the abnormal mutants. Immunosurveillance is an intellectually satisfying thesis which of its very nature is not open to direct testing. There is general agreement that some form of surveillance occurs continuously, but the points of debate are whether immunological rejection is necessary, rather than elimination by non-immunological mechanisms, and whether it has specificity. There is now evidence both for and against these contentions. Recently Prehn (1972) has suggested that stimulation of the immune response may encourage tumours to develop. It may be that several types of surveillance against tumours are operational and only one is mediated through the immune system.

Escape from surveillance

That tumours develop in animals and man and grow progressively and kill the host is an all too common observation in clinical practice. If immunosurveillance exists there must be escape mechanisms which protect tumour cells:

Tumour antigenicity; immunoresistance; sneaking through; vascularization; genetic factors; immunosuppressants; anergy; blocking factors.

Tumours which arise spontaneously seem to be considerably less antigenic than induced ones. Immunosurveillance may be highly efficient in destroying antigenic tumours but may be ineffective against other tumours. Immunoresistance may develop when antigenic autochthonous tumours are exposed to immunological reactions that do not entirely eliminate them. The situation is analogous to bacteria developing resistance to antibiotics. The concept of sneaking through is based on the observations of Old and others (1962). They found that medium-sized inocula of antigenic tumour cells fail to grow in a sensitized animal, but a large dose of tumour cells overwhelms the immune mechanism and grows progressively. Furthermore, a small number of cells can also grow to an irreversible tumour colony before an immune reaction is mounted and this is "sneaking through". It may be that vascularization is the time when the nascent tumour colony becomes invulnerable to immunological attack. Tumour vascularization occurs by an ingrowth of host vascular channels into the tumour and, once established, rapid growth of the tumour occurs (Folkman, 1978).

The successful escape of tumours may result from changes in the host. The response to various antigens, including tumour antigens, can be genetically determined. Exogenous administration of immunosuppressive drugs can diminish host immune response and increase tumour incidence (Penn, 1975). However, patients with tumours show a non-specific depression of immune responses or anergy. The mechanisms causing this are not clearly understood, but may include suppressor lymphocytes and circulating serum factors (blocking factors), which inhibit the usual interaction of host defenses and tumour cells.

Tumour destruction

Tumour immunity is frequently assumed to be a variant of that found in transplantation and, therefore, mediated by the same mechanisms. However, the immunological mechanisms of tumour cell destruction are not completely known and there is disagreement about the relative roles of the separate components of the immunological apparatus in this process. It has not been possible to implicate any one cytotoxic mechanism in the immune elimination of tumours and different mechanisms seem to dominate in varying situations. The importance of T lymphocytes is well established, but there is considerable evidence for other cytotoxic cells (Woodruff, Dunbar and Ghaffar, 1973). One such mechanism comprises cells which have no direct affinity for target cell antigens, but are triggered to kill by antigens bound to the target cells. The cells involved in such antibody-dependent cytotoxicity (ADCC) are not clear. Antibody (from B lymphocytes) may be involved alone or in the presence of complement for tumour cell destruction. Another type of serum that promotes cytotoxicity has been termed unblocking serum by Hellstrom and colleagues (1971), and it is thought to represent the interaction of free antibody with blocking complexes.

The role of phagocytes in tumour destruction is not clear, but resistance of animals to tumour parallels reticuloendothelial phagocytic activity. Although stimulation of reticuloendothelial function protects against some tumours the biological mechanisms underling these observations are not clear. Macrophages certainly exert a critical role initiating and maintaining immune reactions (Feldman and Palmer, 1971). Apart from processing antigen for lymphoid cells, phagocytic cells may be a significant effector mechanism in tumour destruction (Evans and Alexander, 1972). Phagocytic cells have other functions that may be important for control of tumours: they are essential for the response of lymphocytes to some mitogens and, by removal of the blocking factors from the circulation, they may play an important role in restoring the balance between host defences and tumour cells.

Immunotherapy

Immunoprophylaxis is the induction of resistance to tumour before its development and immunotherapy is the treatment of established tumours by immunological methods. In laboratory animals immunoprophylaxis has been encouraging. In humans this has not been practised in the true sense, although Rosenthal and colleagues (1972) showed that vaccination with B.C.G. protected children against the subsequent development of leukaemia. When immunological treatments are used as an adjuvant to conventional methods such as surgery, radiotherapy or chemotherapy to prevent recurrent disease, then immunoprophylaxis and immunotherapy merge imperceptibly.

Immunotherapy results have been disappointing. Treatment may be specific, designed to cope with a particular tumour, or non-specific, when the overall immunological reactivity of the host is changed. Specific immunotherapy can be passive, adoptive or active. Passive therapy involves the use of antisera which may be syngeneic, allogeneic or xenogeneic and then specifically absorbed. Adoptive therapy necessitates the transfer of syngeneic, allogeneic or xenogeneic lymphoid cells from specifically immunized donors. Active immunotherapy aims at increasing the immunogenicity of tumour cell antigens which are weak. Tumour cell antigens can be rendered more immunogenic by changing the dose or route of administration and by alteration of the cells in a variety of ways: physical treatments; viral incorporation; chemical modification; surface changes by enzymes; coupling with immunogens.

Non-specific immunotherapy involves a general increase of immune reactivity. With present knowledge, four methods of stimulation of host responses are available which might retard tumour growth:

(1) Increased or improved localization of cytotoxic antibody.
(2) Suppression of blocking factors.
(3) More effective macrophage activity.
(4) Improved cell-mediated immunity.

A combination of specific and non-specific therapy has been the commonest approach to immunotherapy in clinical practice (Mathe, 1971). The rationale for the treatment is that non-specific adjuvants will generally boost the immune response including any reaction to synchronously administered exogenous tumour antigens.

Immunotherapy of human tumours has a long and undistinguished history. The majority of studies have so far been uncontrolled.

Allograft rejection

At one time it was thought that the immunological mechanisms involved in tumour cell rejection were similar to those involved in organ graft rejection. Although some mechanism may operate in both situations, it is unlikely that the processes are analogous in detail.

The cellular basis of immunological reactions to allografts is best worked out in the case of skin grafts in animals when genetically defined models can be used. The process has an afferent pathway which involves sensitization of lymphocytes by contact with the graft or, alternatively, soluble graft products reach the draining lymph nodes. It has been established that the integrity of the regional lymphatics is an important requirement for the afferent pathway of graft sensitization, although lymphatics do not seem to be required for rejection. In the central phase, sensitized lymphocytes reach the regional nodes and proliferate. The population of cells sensitive to skin allografts belongs to the recirculatory lymphocyte pool and a specially sensitized population probably results from proliferation at first in the regional node, which is then continued in the more distant nodes. In the efferent phase, cells of the recirculating pool, many of them newly formed by proliferation either in the lymph nodes or bone marrow, subsequently reach the allograft. At that site there is initial massive recruitment of normal unsensitized B and T cells by the sensitized cells. Secondly, there is an attraction of macrophages into the area, probably as a result of the release of macrophage inhibition factor by sensitized lymphocytes.

After kidney grafting it is the combination of antibody acting on the vasculature of the kidney, together with cellular infiltration, which produces the characteristic histological and pathological features of hyperacute, acute and chronic rejection.

Hyperacute rejection is the counterpart of the secondary immune response and it occurs in patients who have already been sensitized to specific donor antigens. In extreme cases the kidney becomes cyanosed shortly after implantation, even on the operating table. Histologically, there is thrombosis of the medium and smaller arterioles with parenchymal haemorrhage and cellular infiltration. Acute rejection is characterized by a diffuse infiltration of the entire parenchyma by small and large lymphocytes, macrophages and small numbers of plasma cells. There is an especially heavy infiltrate around the smaller afferent arterioles. Chronic rejection may occur over a long period of time and it is characterized by progressive deterioration in renal function. There is progressive fibrosis and narrowing of vessels as a result of fibrin deposition.

Clinical renal transplantation

Attempts to transplant the kidney experimentally began in earnest in 1902, when Ullman reported the first successful experimental organ transfer using Payr's cannulae to achieve vessel anastomosis. The same year, Carrel described his "vascular patch" which, since that time, with some minor modifications, has been used for revascularizing organ transplants. In 1905, Floresco grafted kidneys orthotopically and subsequently he joined them to the femoral vessels and obtained good urine flow through a cutaneous fistula. In 1955, nine kidney transplants were reported between non-identical donors and recipients (Hume et al., 1955). Despite the lack of tissue-typing and immunosuppression, four of these grafts functioned for between 30 and 120 days. The original technique in humans was to anastomose the donor renal vessels to the femoral vasculature and to bring the ureter as a cutaneous ureterostomy.

In parallel with the development of techniques for vascular anastomosis and transfer of organs, there was rapid development of transplantation immunology. A new era followed the experiments of Medawar and his associates, who clarified the mechanisms of immunological rejection. It was not long before irradiation and antimetabolites, which showed promise in animal experiments, were applied to man to reduce rejection. In 1959, whole body irradiation to a recipient afforded the first prolonged survival of a kidney allograft.

Clinical renal transplantation is now an accepted and standard form of treatment for patients with chronic renal failure. Since 1963, 25 108 transplants have been registered with the American College of Surgeons–National Institutes of Health registry. In the United Kingdom 600 transplants are undertaken annually. Of transplants carried out in this country and Europe, 10% are from living related donors. In the United States this figure approaches 40–50%, although the introduction of health care programmes has increased the number of cadaver transplants. In contrast, in Australia only 2% of transplants are from living related donors.

Most rejection episodes and most recipient deaths occur in the first 2 years after transplantation, although later complications do occur. Results from the transplant registry show 2-year survival with a functioning transplant to be 74% after a sibling kidney transplant, 68% after receiving a kidney from a parent and 47% after cadaver kidney transplant. Individual units, with wide experience, or rigid criteria for accepting patients, or insistence on using only "beating heart" cadaver kidneys, report better results. Patient survival is considerably better and the corresponding survivals at 2 years are 83%, 81% and

64%. During the past few years, functioning kidney survival has not improved and this reflects the lack of progress in overcoming rejection. Despite this, results are comparable to, or better than, those obtained in the treatment of many of the major cancers and, moreover, many of the patients are young adults with dependents. In contrast, patient survival has consistently improved, probably because of the early abandonment of failing transplants, before the effects of excessive immunosuppression supervene. This policy is encouraged by the good results of second and subsequent transplants.

With increasing experience, transplantation is being offered to a wider group of patients with renal failure. Transplantation in patients with metabolic and systemic diseases is increasingly common and the recent reports for diabetic patients show that the procedure is worthwhile in this group (Najarian et al., 1973). Certain groups of patients have a better prognosis: for example, those with renal cystic disease. Although some diseases recur in the transplant (for example amyloid and dense deposit disease), they do not necessarily impair renal function significantly.

The full potential of transplantation surgery is at present hampered by the lack of donor organs. There are 1200 patients (the majority between 30 and 50 years) on file awaiting transplantation and it is estimated that 2500 patients could benefit from transplantation annually. Each year 600 kidneys are transplanted in Britain. Even a proportion of the annual 6000 fatal road traffic accidents, let alone those patients dying of cerebrovascular disease or cerebral tumours, would totally satisfy the transplantation needs of the country.

Because of the shortage of kidneys, there is no doubt that units use kidneys which, in a more affluent situation, might have been turned down. It has been shown that 17% of kidneys transplanted in this country never function, many because of excessive warm ischaemia (Nelson and Tovey, 1974). In the United States and some parts of Europe, primary failure as a result of ischaemic damage is very rare, since the public has accepted the concept of brain death and most kidneys come from patients with irreversible brain damage but with an intact circulation.

Whilst the survival of patients receiving cadaver renal transplants has steadily and significantly improved, functioning-graft survival has not changed for several years. This results from the high frequency of rejection and the lack of any significant change in immunosuppressive regimes for the past decade. Prednisone and azathioprine, with all of their attendant problems, are still the cornerstones of immunosuppression. In experimental studies heterologous antilymphocyte serum (ALS) is the most effective agent for the abrogation of cellular immunity. The remarkable ability of ALS to suppress allograft rejection in both small and large animals has generated much enthusiasm for its use in clinical transplantation. Unfortunately, despite its use for several years as an adjuvant immunosuppressive, its clinical effectiveness is still not established. In the United States, of 100 major centres, 67% used it and half of these thought it to be beneficial (Monaco, Campion and Kaprick, 1977). The few controlled trials of the agent have given equivocal results (Launois et al., 1977).

Other agents also have been studied recently. The importance of vascular changes in graft rejection is well established and agents affecting platelet function have been investigated. In experimental allografts, sodium salicylate, acetylsalicylic acid, heparin and dicoumarol all prolong graft survival. In clinical studies, dipyrimadole improved vascular lesions, but did not improve results. Cyproheptadine is a safe antihistamine with antiserotonin activity and appears to be a useful drug when used in combination with conventional treatment (Rattazzi, Simmons and Najarian, 1977). The antihelminth, niridazole, has been shown to prolong a skin allograft survival in rodents and it is immunosuppressive in man. However, side-effects are common and current studies are directed to finding a non-toxic, immunosuppressive metabolite (Salaman et al., 1977). Cyclosporin A is a new immunosuppressive which requires further clinical evluation.

Because of the complications of pharmacological immunosuppression, the search for a specific form of allogeneic unresponsiveness that does not interfere with the remainder of the host's immunological defences is the central goal of transplantation research. The dividing lines between classical tolerance, enhancement and blocking have become increasingly tenuous. Although the classical experiments of Billingham, Brent and Medawar (1955) on neonatal tolerance demonstrated the principles involved, approaches which may be more clinically relevant utilize irradiation and bone-marrow transplantation. Other approaches to specific unresponsiveness involve the use of antisera against tissue incompatibility antigens, but more experimental work is needed before these techniques can be applied routinely to clinical practice.

Inadvertently, clinicians may have stimulated a degree of unresponsiveness by the use of blood transfusions. Originally it was feared that transfusion might presensitize patients and so decrease the likelihood of a successful subsequent transplant, for it has been shown that sensitized patients have a distinctly lower transplant survival rate (17% at 1 year) than those who are not sensitized (59% at 1 year). However, Opelz, Sengar and Mickey (1973) have suggested that transplant recipients who have received blood transfusions have a better chance of successful grafting than those who have never been transfused. More recently, Fuller and colleagues (1977) have shown that frozen blood is just as effective in promoting graft survival, but the frequency of sensitization is only 4.8% compared with 50% after whole blood. When the beneficial effects of transfusion and the detrimental effects of sensitization are combined, the theoretical chances of a successful graft at 1 year are 27% for those receiving no blood, 34% for those given whole blood and 57% after frozen blood. Further studies to determine the effects of different numbers of transfusions and the timing and relationship to grafting are required.

The mechanisms involved in these observations are not clear. Originally it was thought that some individuals are indiscriminate responders and others non-responders and transfusion was acting as a sorting mechanism to identify these groups. The alternative possibility of specific immunological enhancement is more attractive.

Immunogenetics

The immunological reaction to transplants is directed against genetically determined foreign substances, probably glycoproteins, on the surfaces of transplanted cells. Apart from ABO antigens, which may act as strong transplantation antigens, the most important of these substances are antigens of the major histocompatibility system (MHS) which are coded for in the MHS region (fig. 1). In this region there are three subloci which code for three serologically determined, SD (formerly HLA, Human Leukocyte Antigen) antigens and at least two lymphocyte determined, LD (formerly MLC, mixed lymphocyte culture) antigens. Serologically determined antigens are defined by sera from sensitized patients. By exhaustive testing of panels of antisera against panels of normal lymphocytes, using cytotoxicity or agglutination assays, it has been possible to develop patterns of specificity and gene frequency. LD antigens stimulate T cells in MLC but detection of surface immunofluorescence may aid direct typing for these specifications.

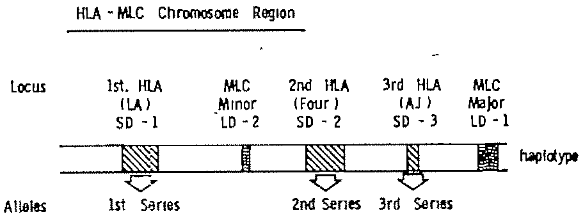

FIG. 1. MHS phenotype inheritance. Antigens determined by the MHS are inherited in Mendelian fashion, with no allelic exclusions.

It is known that tumour allograft and probably organic graft rejection require interaction of both LD and SD antigens with both T and B cells. It is thought that T cells are stimulated primarily by LD antigens. In contrast, B cell antibodies, B cell cytotoxicity and ADCC are directed against SD determinants. In graft rejection the usual sequence of rejection is that T cells are stimulated by LD, then stimulated T cells together with B cells programmed to react against SD determinants interact to cause these cells to mount a reaction against SD.

Clinical histocompatibility testing

The relative influences of SD and LD compatibility matching on the ultimate outcome of renal allotransplantation is currently under investigation (Sachs, 1977). There is some suggestion that, in patients matched for LD antigens, a mismatch for SD antigens may be important only if the patient has already been sensitized to SD antigens. Although the presence of MHS compatibility is important for graft survival, it is interesting that skin graft survival in SD identical members of the *same* family survive much better than SD identical individuals from different families. This suggests that there may be many minor determinants of histocompatibility, not coded for by MHS region, which are also important for graft rejection.

Recently there has been observation of an association between the MHS and disease susceptibility. During the past 10 years, about 40 diseases have been reported to have their susceptibility associated with or linked to tissue type; some of these are shown in table I. In establishing these associations, several

TABLE I. *Diseases having susceptibility associated with or linked to tissue type*

Disease	Antigen	Antigen frequency (%) patients/control	Relative risk
Ankylosing spondylitis			
Caucasoid	B27	90/8	88
Haida Indian	B27	100/51	34
Japanese	B27	77/0	306
Reiter's syndrome	B27	78/8	36
Post-salmonella arthritis	B27	67/9	18
Post-Yersinia arthritis	B27	79/9	24
Rheumatoid arthritis	Dw4	36/16	3
Addison's disease	B8	50/23	4
	Dw3	70/15	11
Haemachromatosis	A3	78/27	10
	B14	26/3	9
Multiple sclerosis	A3	36/26	2
	B7	34/25	2
	Dw2	67/18	7
	Group 4 (B cell)	84/33	11
Diabetes mellitus (juvenile onset)	B8	37/22	2
	Bw15	23/15	2
Chronic active hepatitis	B8	44/20	3
	B8/B8	29/3	13
Graves' disease			
Caucasoid	B8	42/24	3
Japanese	Bw35	57/21	5
Psoriasis nonspecificata	B13	15/5	4
	Bw16	16/3	4
	Bw17	28/7	5
Acute lymphocytic leukaemia			
Newly diagnosed	A2	53/44	
> 1500 days survivors	A2	83/44	

principles are important. First, because antigen frequencies depend upon ethnic background, there must be adequately matched controls. In diagnosis, subgroups may be important. For example, there is no association between diabetes and tissue type, but if juvenile onset, insulin-dependent diabetes only is considered, an association is detected. Statistical analysis is imperative, and in this respect the association of a disease with one of 20 antigens will occur by chance alone. A distinction must also be made between association and linkage. Association is demonstrated in population studies of unrelated individuals when two particular traits occur together at a frequency different from that predicted by chance alone. Linkage cannot be proven by population studies, but must be shown in studies in families in which joint segregation of two traits can be demonstrated in a consistent pattern. The intensity of an association is measured by the relative risk (RR):

RR = (number of patients negative for the antigen) × (number of controls positive for the antigen).

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EFFECTS OF ANAESTHESIA AND SURGERY ON IMMUNE STATUS

B. WALTON

There is increasing evidence that exposure to anaesthesia and surgery alters many facets of immunocompetence. In this paper, the evidence will be reviewed briefly—with particular reference to possible clinical implications for anaesthetic practice.

Immune mechanisms

Protection against foreign organisms involves a battery of non-specific resistance mechanisms interrelated with the two limbs of specific immunity. Non-specific mechanisms include the protection of alveoli by ciliated respiratory epithelium, bactericidal acids in sweat and sebaceous secretions and both intra- and extra-cellular bactericidal enzymes (lysozymes). Phagocytosis, a most important non-specific mechanism, is encouraged by the acute inflammatory response at the site of infection which allows the accumulation not only of phagocytes but also of bactericidal factors such as properdin. Several immune mechanisms are augmented by the complement system. This system of at least nine proteins is activated either by antigen–antibody complexes or by properdin or bacterial lipopolysaccharides ("alternate pathway"). Activation results in increased capillary permeability, the attraction of polymorphonuclear leucocytes and the enhancement of phagocytosis.

Two populations of leucocytes, designated B and T lymphocytes, are responsible for specific immunity. B lymphocytes become plasma cells on contact with antigen and produce antibodies (immunoglobulins) which result in humoral (or antibody-mediated) reactions. T lymphocytes, on the other hand, become sensitized lymphoblasts on contact with antigen and cell-mediated immune responses result. Co-operation exists between the two "limbs" of specific immunity and the reactivity of B and T lymphocytes is enhanced by, for example, the "processing" and representation of antigen (non-specifically) by macrophages.

The lymphocyte transformation test (LTT) and leucocyte migration inhibition test (LMIT) are used as *in vitro* indices of lymphocyte reactivity. Both tests rely on the recognition, by previously sensitized lymphocytes, of an antigen introduced into the culture medium. In the LTT, the resulting transformation into lymphoblasts is usually monitored by the uptake of tritiated thymidine by the transforming cells. In the LMIT, recognition of antigen results in the release of migration inhibition factor (MIF) which inhibits the migration of leucocytes from the open end of a capillary tube. The area of migration can be mapped by planimetry. For assessment of variations in lymphocyte responses in the peri-operative period (by the LTT), a standard dose of a non-specific mitogen phytohaemagglutinin (PHA) is often included in the culture medium. Alterations of lymphocyte transformation in the presence of a standard dose of PHA are taken to indicate variations in lymphocyte reactivity. Readily available texts on basic immunology (Roitt, 1974) and immunological methods (Gell and Coombs, 1975) are recommended for further reading.

Peri-operative factors affecting immune status

Anaesthetic agents may have both direct and hormone-mediated effects on immune mechanisms, although it may be that the longer-term non-specific hormonal effects of the "stress" response to anaesthesia and surgery may have far more profound implications.

Changes in hormone concentrations may influence immune status in many ways. The postoperative leucocytosis following diethyl ether anaesthesia reported by early workers (Chadbourne, 1899; Mann, 1916) relates to the sympathomimetic effects of the agent, and it has been shown that increased catecholamine concentrations are associated, not only with increases in the numbers of circulating lymphocytes and neutrophils, but also with alterations in distribution and mobilization (Dougherty and Frank, 1953). Steroids also cause neutrophilia, but may have toxic effects on lymphocytes (Michael, 1949). In addition, in animals, steroids depress protein synthesis (Kidson, 1967), mitosis and thymus cell metabolism (Young, 1969). Whether such effects occur at the concentrations found clinically in the period after

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operation is open to doubt, although depressed phagocytosis is demonstrable in patients on steroid therapy (Crepea, Magnin and Seastone, 1951).

In addition to these major factors, peri-operative immune status may be adversely affected by other facets of treatment. For example, several antibiotics, including streptomycin (Kreuger, 1965) and tetracycline (Majeski, McClellan and Alexander, 1975), have been shown to alter immune status (although massive doses in animals were involved) and the use of chloramphenicol is associated with prolonged skin graft survival (Weisberger, Daniel and Hoffman, 1964). *In vitro* lymphocyte reactivity is affected by salicylates (Crout, Hepburn and Ritts, 1975) and blood transfusion (Schechter, Soehnlen and McFarland, 1972) and concurrent, perhaps unrecognized, viral infections may depress specific immunity (Notkins, Mergehagen and Howard, 1970). It has been shown, for example, that mortality among mice infected with murine hepatitis virus is increased by exposure to halothane, and this may reflect a combination of immunosuppressive factors (Moudgil, 1973).

Finally, it must be remembered that changes being investigated and perhaps being attributed to various peri-operative factors may be superimposed on normal cyclical variations in phagocytosis (Alexander, Dionigi and Meakins, 1971), and lymphocyte reactivity (Simpson et al., 1973).

Anaesthetics, cell division and leucopenia

In contrast with the postoperative leucocytosis related to the hormonal effects of anaesthesia and surgery are the reports that exposure to anaesthetic agents may produce leucopenia. For example, transient leucopenia has been reported following anaesthesia with barbiturates, diethyl ether and chloroform in some species (Schweitzer, 1932; Smith, Oster and Snydel, 1948; Usenik and Cronkite, 1965) and this has been attributed either to direct toxicity or to redistribution of leucocytes. The variations in white cell count seen during, say, halothane anaesthesia in man (Humphrey, Amerson and Frederickson, 1969) may reflect the interplay between direct transient effects of the agent itself on the one hand, and hormone-mediated increases in cell counts on the other.

Prolonged exposure to many agents, including hydrocarbons (Aldrete and Virtue, 1967), nitrous oxide (Lassen et al., 1956) and halothane (Bruce and Koepke, 1966), results in leucopenia. Exposure of bone marrow cells to these agents arrests their development (and protects them from the effects of chemotherapy) (Bruce, Lin and Bruce, 1972)—a manifestation of deleterious effects on the cell cycle. Many anaesthetic agents, including nitrous oxide (Kieler, 1957), trichloroethylene and chloroform (Ostergren, 1944), had been shown to arrest mitosis at the metaphase stage (rather like the picture seen with colchicine and thus known as c-mitosis), and narcotics and tranquillizers have antimitotic effects (Simon, 1964). More recently, halothane has been shown not only to arrest cell division at the metaphase stage (Nunn, Lovis and Kimball, 1971) but also to prolong the DNA synthetic and post-synthetic phases (Bruce and Taurig, 1969; Sturrock and Nunn, 1975). It seems, therefore, that the leucopenia seen after prolonged exposure to anaesthetic agents results from adverse effects at many stages of the cell cycle as part of the overall depression of cellular metabolism.

Non-specific resistance mechanisms

Many non-specific mechanisms are adversely affected by exposure to anaesthesia and surgery. Tracheal mucociliary flow is depressed during anaesthesia (Forbes, 1976) and this effect is heightened by the administration of atropine (Annis, Landa and Lichtiger, 1976) or high inspired oygen concentrations (Sachner et al., 1975). Pulmonary bactericidal activity in the mouse is adversely affected by exposure to cyclopropane and methoxyflurane (Goldstein et al., 1971). The depression of phagocytosis seen after operation results from many factors and seems proportional to the duration of surgery (Donovan, 1967). Phagocyte mobilization is directly depressed by halothane (Bruce, 1967) and diethyl ether (Bruce and Wingard, 1971), as is the chemotactic attraction of phagocytes and lymphocytes by a variety of agents (Moudgil et al., 1977). Margination (Pickerell, 1938) and transvascular diapedesis (Magalini and Scrascia, 1974) are also inhibited, and phagocytosis itself is directly depressed by exposure to diethyl ether (Graham, 1911) and halothane (Bruce, 1967). These effects may also relate to alterations in serum factors. Properdin concentrations are reduced after operation (Benson et al., 1956) and the opsonic stimulation of phagocytosis is reduced by diethyl ether (although much greater reductions are seen during anaesthesia *and* surgery (Saba, 1970)). The fact that phagocytosis is depressed following non-surgical stress (McCabe et al., 1973) and reticuloendothelial function is diminished in "shock" (Alexander, Hegg and Altmeier, 1968) underlines the importance of the "stress" component of anaesthesia and surgery. This effect presumably relates to alterations in hormone concentrations, as it has been shown that large doses of steroids inhibit phagocytosis (Nicol, Vernon-Roberts and Quantock, 1965). Other possibly relevant factors such as concurrent viral infections (Larson and Blades, 1976), antibiotics (Majeski, McClellan and Alexander, 1975) and local lignocaine infiltration (Cullen and Haschke, 1974) may also adversely affect phagocytosis itself or the chemotactic attraction of phagocytes. It seems likely that the overall depression of non-specific resistance mechanisms, possibly more related to the degree of surgical "stress" rather than to anaesthesia *per se*, may render patients more likely to develop clinical infections during the period following surgery.

Specific immune responses

The function of both B and T lymphocytes is depressed by anaesthesia and surgery. The population of B lymphocytes is reduced after operation (Slade et al., 1975) and prolonged exposure to several anaesthetic agents reduces the number of splenic antibody-producing cells (Wingard, Lang and Humphrey, 1967; Humphrey, Wingard and Lang, 1969) and antibody production. Preformed antibodies (immunoglobulins) are, in general, unaffected (Cohen, 1972), although transient decreases in IgG have been reported (Werner and Odenthal, 1967). Reductions in antibody-producing cells have also been reported following burns (Alexander and Moncrieff, 1967) and antibody depletion is seen after a variety of injuries (Cuthbertson, Tilstone and Green, 1969; Ritzmann et al., 1969)—although a burned patient seems able to mount antibody responses (Jones and Lowbury, 1963). The fact that anaesthesia alone, in animals, depresses B lymphocytes minimally (Viljanen et al., 1973; Cooper, Irvine and Turnbull, 1974), suggests that the "stress" component of anaesthesia and surgery is the most important factor in this respect also.

Using the LTT and LMIT, T lymphocyte function has been shown by most workers to be depressed after operation (Riddle, 1967; Park et al., 1971). The T cell population decreases during anaesthesia and surgery (Slade et al., 1975) and, after operation, T cell responses in mixed lymphocyte culture (Slade et al., 1975) and to tumour-derived antigens (Cochran et al., 1972) are diminished. Although the PHA responsiveness of lymphocytes is decreased following induction of anaesthesia (before the start of surgery) (Espanol, Todd and Soothill, 1974), the degree of depression of T lymphocytes after operation is proportional to the degree of surgical stress (Cullen and van Belle, 1975). Various conflicting reports regarding this facet of immune function may relate, in part, to the variable effects of premedication. Apparent augmentation of *in vitro* T-lymphocyte responses have been seen following premedication and postoperative analgesia in some patients (B. Walton and colleagues, unpublished results). It is possible that increased concentrations of hormones in patients who are anxious or in pain, or both, may depress lymphocyte reactivity and result in falsely low "baseline" levels of preoperative T lymphocyte function being recorded. Clearly, hormone concentrations play an important part in T cell reactivity, as lymphocyte responsiveness is depressed by steroids (McIntyre, Eurenius and Holland, 1967) and the practical implications of depressed T-cell function are seen as prolonged skin graft survival (Kay, 1957) and decreased skin reactivity (Rapaport et al., 1968) following various forms of "stress". Other factors such as blood transfusions (Schechter, Soehnlen and McFarland, 1972) and sedatives such as chlorpromazine (Pisciotta, Westring and DePrey, 1967) may have minor effects but, once again, the most important contribution to peri-operative T lymphocyte depression is made by the hormonal aspects of the "stress" response.

Infections after operation

Infections developing during the period after surgery account for much of the estimated 15% (Johanson and Sanford, 1968) infection rate among hospital patients. Several factors have been shown to be associated with increased infection rates, including advancing age (Davidson, Clark and Smith, 1971), obesity (Cruse and Foord, 1973), poor nutritional status (Dhillon, Maclean and Meakins, 1975) and, most significantly in the context of this review, prolonged surgery (Jepsen, Larsen and Thomsen, 1969; Altmeier, 1972), and steroid therapy (Co-operative Study, 1964). There are few data relating postoperative infection rates to different anaesthetic techniques and, as it is well recognized that, in several species, susceptibility to infection is increased following various types of trauma (Alexander, 1968; Conolly et al., 1969), it seems likely that the "stress" component of anaesthesia and surgery plays a significant part in the development of infections in the period after operation. Nonetheless, anaesthetic agents have been studied in this respect, and early studies involving diethyl ether, chloroform and other agents were contradictory. In some species, susceptibility to bacterial and viral infection was increased by exposure to these agents (Snel, 1903; Rubin, 1904), while other workers reported a protective effect of diethyl ether, nitrous oxide, barbiturates, morphine, and tribromethanol in experimental tuberculosis (Brown and Petroff, 1919), tetanus (Kaspar, 1928) and botulinus (Bronfenbrenner and Weiss, 1924) infections. It has been suggested that, in the case of diethyl ether, the *in vivo* protective influence afforded in some viral infections parallels the *in vitro* "ether sensitivity" of these viruses and, in the treatment of canine distemper, the use of diethyl ether has been advocated (Donovan, 1968). More recently, however, exposure to halothane has been shown to increase morbidity and mortality among mice with various bacterial and viral infections (Bruce, 1967; Moudgil, 1973), and although inhibitory effects of anaesthetics on bacterial division rates have been reported (Metha, Behr and Kenyon, 1974), it is unlikely that any such theoretically beneficial short-term effect would detract from the overall immunosuppression resulting from exposure to anaesthesia and surgery.

Malignancy

Resistance to malignant disease requires immunocompetence (Gatti and Good, 1970), and both immune deficiency and immunosuppressive therapy are associated with an increased frequency of malignant disease (Fialkow, 1967; Penn et al., 1969). In animals, immunosuppression both increases the oncogenic response to chemical (Reiner and Southam, 1967) and viral agents and decreases tumour-directed cell-mediated reactions (Silk, 1967; Nelson, 1969). In the light of this, it seems feasible that the immunodepressant aspects of exposure to anaesthesia and surgery might render more likely the spread of malignancy after operation. Indeed, incidental minor surgery in patients having survived long after removal of a primary tumour may be followed by widespread growth of metastases (Gordon-Taylor, 1948). It is of interest that postoperative *in vitro* lymphocyte responses to both mitogens (Han, 1972) and antigens (Cochran et al., 1972) are reduced in malignant disease and that, ironically, the degree and duration of immunosuppression after operation may be greater than in patients without malignancy (Park et al., 1971).

Contradictory reports on the influence of anaesthetic agents themselves on experimental oncogenesis have appeared. In some cases, the development of metastases and the success-rate of transplanted tumours were enhanced by anaesthesia (Gaylord and Simpson, 1916; Agostino and Clifton, 1964) whereas other workers have reported insignificant effects of exposure to diethyl ether (Fisher and Fisher, 1959) and halothane (Cullen and Sundsmo, 1974). Although it has been shown that cell-mediated cytotoxic reactions are inhibited by halothane and nitrous oxide (Cullen, Duncan and Ray-Keil, 1976), it seems likely that, if anaesthetic agents have *in vivo* effects of this nature, they are minor and relatively short-lived. Similarly, any intra-operative depression of the metabolism of malignant cells by anaesthetic agents is unlikely to alter significantly the postoperative course. In relation to malignancy, the stress of anaesthesia and surgery seems much more important, as surgical stress encourages the development of malignancy in animals (Gottfreid, Molomut and Skaredoff, 1961), as does the administration of steroids (Baserga and Shubik, 1955).

Choice of anaesthetic regime

In general, the hormonal aspects of the stress of anaesthesia and surgery are clearly more important with regard to immunosuppression after operation than anaesthetic regimes *per se*. It remains relevant, however, to ask whether, in patients with malignant disease (who are ill-served by any unnecessary depression of immune status), any anaesthetic regime is less depressant than others. The studies that have appeared suggest little difference between regimes in this respect. Although greater depression of B and T lymphocytes after operation has been reported following diethyl ether, compared with halothane anaesthesia (Jubert et al., 1973) (presumably related to the hormonal effects of the former agent), similar degrees of depression have been seen following herniorraphy under spinal or nitrous oxide–halothane anaesthesia (Bruce, Behbahani and Land, 1976). A recent comparison of immune status after surgery in patients undergoing a variety of operations under halothane–nitrous oxide, thiopentone–droperidol–fentanyl or spinal regimes also showed minimal differences (Ryhanen, 1977) and the present author has also seen a similar degree and duration of lymphocyte depression following surgery when comparing both inhalation and total i.v. techniques (Walton and colleagues, in preparation). The findings mentioned earlier regarding apparent augmentation of lymphocyte responses following premedication and analgesia after surgery suggest that a more aggressive approach to the relief of pain and anxiety after operation, at least in patients with malignant disease, may have beneficial immunological consequences.

SUMMARY

The immunological implications of anaesthetic practice relate to the possibility that exposure to anaesthesia and surgery, by depressing a variety of both non-specific resistance mechanisms and specific immune responses, renders patients more liable to infections and the spread of malignancy in the period after operation. A review of the literature suggests that, although various anaesthetic agents themselves depress immune responses, the effects are short-lived and of minor importance when compared with the effects of the hormonal aspects of the stress response. A more aggressive approach to relief of pain and anxiety may be beneficial from the immunological point of view.

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IMMUNOLOGICAL REACTIONS TO BLOOD AND BLOOD PRODUCTS

P. HILGARD

It is estimated that approximately one-third of all blood transfusions are given during anaesthesia (Van Dijk and Kleine, 1976), and improved cross-matching techniques have reduced the frequency of adverse reactions to less than 2%. Most of these reactions are caused by immunological phenomena (Ahrons and Kissmeyer-Nielsen, 1968), and their frequency is shown in table I.

TABLE I. *Distribution of transfusion reactions according to Ahrons and Kissmeyer-Nielsen* (1968)

Transfusion reaction	Frequency (%)
Immunological reactions	
Febrile reaction	75.40
Allergic reaction	13.62
Delayed haemolytic reaction	3.76
Immediate haemolytic reaction	1.10
Total	93.88
Non-immunological reactions	
Overload	1.99
Hepatitis	1.55
Citrate intoxication	0.81
Miscellaneous	1.77
Total	6.12

All blood cells possess inherited antigens; their pattern is specific for any individual or groups of individuals, and remains constant throughout life. Although the majority of the antigens were first recognized in association with blood cells, it is now evident that many of them are also found in other tissues and in body fluids, and specific antigens have been demonstrated in plasma. Antibodies against blood cell or plasma antigens are usually formed when an antigen not present on the cells or in the plasma is introduced parenterally. There are, however, a few naturally occurring antibodies which are regularly found in human serum without any obvious previous exposure to the corresponding antigen. Most of these antibodies, whether naturally occurring or immune, are either IgM or IgG immunoglobulins. However, occasionally IgA antibodies may be found. Naturally occurring antibodies are "cold" antibodies, the *in vitro* antigen–antibody reaction being stronger at low temperatures, whereas most immune antibodies are of the "warm" type as they react readily at 37 °C.

RED CELL ANTIGENS AND THEIR ANTIBODIES

Since the discovery in 1901 of the ABO blood group antigens and their corresponding antibodies, numerous other inheritable red cell antigens have been described, and more than a dozen antigen systems have been characterized. There is a very little information about the biochemistry of most of the red cell antigens. The erythrocyte antigen–antibody interaction is usually detected by haemagglutination techniques, whereas soluble blood group antigens in body fluids or tissue extracts are characterized by antibody neutralization tests. Most common blood grouping antisera are derived from human sources. The following description of red cell antigens and antibodies will divide the blood group systems into two major groups: (1) antibodies occurring in the absence of exposure to blood from another person, that is "naturally occurring antibodies" and (2) antibodies that form as the result of blood transfusion or pregnancy, that is "acquired antibodies".

Blood group systems with naturally occurring antibodies

ABO antigens and antibodies. The ABO blood group system was the first to be discovered, and it is still clinically the most important, since all people produce anti-A or anti-B antibodies, or both, when their red cells lack the corresponding antigens. For routine purposes only two antisera, anti-A and anti-B, are sufficient to characterize the ABO antigens. In an AB person neither anti-A nor anti-B is found in the serum, whereas a group O person normally shows anti-A and anti-B activity. A group A person has anti-B antibodies, and a group B person has anti-A antibodies. In some cases it may be useful to distinguish between A_1 and A_2 types and the additional

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use of anti-A_1 antisera allows further division of the AB blood group into A_1B and A_2B: thus the classical ABO system consists of six phenotypes: O, A_1, A_2, B, A_1B and A_2B. It is now recognized that group O red cells can be agglutinated by a specific antiserum called anti-H. The H antigen is present in the red cells of all blood groups, but there are significant quantitative differences between the different groups and the highest antigenicity is being found in blood group O. Antibodies with H specificity occur as weak cold agglutinins, and they do not normally represent a transfusion hazard. The very rare O_h (Bombay) phenotype lacks the A, B and H antigens, thus a potent anti-H as well as anti-A and anti-B are found in the plasma. If a patient of the Bombay type requires blood transfusion, the only compatible donors are persons of the same rare type.

The Lewis blood group system. The Lewis system is a complex blood group system with many obscure features in its genetics and serology.

The presence of these antigens on the erythrocyte is an expression of plasma antigens absorbed by the red cells. The antibody specificity is often complex, and some of the Lewis antibodies can cross-react with antigens of the ABO system. The presence of anti-Le^a is an uncommon potential transfusion hazard. Only about 20% of Caucasian donors are Le^a (a+/b−). Not all of these have anti-Le^b in their serum, and this antibody is only weakly reactive. About 5–6% of donors are Le (a−/b−).

The P blood group system. Five phenotypes of the P antigen are known. About 75% of the population possess the antigens P_1 and P on their red blood cells, thus they do not have serum antibodies against the P system. Twenty-five per cent have only P on their red cells, and correspondingly show anti-P_1 activity in their serum which is often only detectable at relatively low temperatures and is usually of no clinical importance. The remaining phenotypes of the P system ($P_1{}^k$, $P_2{}^k$ and p) are extremely rare. However, when they are demonstrated, compatible blood donors are difficult to find.

The MNSs blood group system. Nine phenotypes are known (MS, MSs, Ms, MNS, MNSs, MNs, NS, NSs, Ns). The antibodies anti-M, anti-N and anti-S are usually naturally occurring antibodies; whereas anti-s never occurs without previous sensitization. The frequency of the various phenotypes varies considerably within different racial groups. Transfusion reactions caused by MNSs incompatibility are extremely rare.

Blood group systems associated with acquired antibodies

Allo-antibodies* are formed in response to transfusions or pregnancy. They usually belong to the IgG class. The two major factors determining the frequency of formation of allo-antibodies are the population distribution of the antigens and their immunogenicity.

The Rhesus system. It is now evident that the Rhesus system is a highly complex blood group system with a large number of different antigenic determinants. The present confusion in the nomenclature of the various antigenic determinants reflects ignorance about the biochemistry and physiology of the antigens. In Europe the Fisher–Race nomenclature is currently widely accepted, in which the five major determinants are called D, C, E, c, e. It was suggested that the Rh loci carry three genes, for instance CDe, cde, cDE or other combinations. Since each parent contributes one chromosome, numerous genotypes can be found. The most frequent genotypes are CDe/cde, CDe/CDe, cde/cde, CDe/cDE, cDE/cde, cDe/cde and cDE/cDE (Race et al., 1948).

These combinations represent the gene frequencies in British subjects and are similar for other Western European populations. Other ethnic groups have different frequencies. The D antigen is the most important Rh determinant, since it has the strongest immunogenic capacities. Fifteen per cent of the Caucasian population lack the D antigen on their red cells (Rh negative) and they have a 50% chance of becoming sensitized after a single transfusion of Rh-positive blood. Anti-D antibodies are found in approximately 80% of subjects who have received repeated transfusions of Rh-incompatible blood. The antigens C, c, E, e are far less immunogenic. Blood donors and patients are initially only typed with anti-D, and if found D-negative, they are additionally typed with anti-C and anti-E. There are some quantitative Rh variants that can cause laboratory confusion. The D variant D^u, often found in black individuals in the complex CD^ue/cde, reacts much more weakly with the usual anti-D antiserum. This antigen is best detected by the indirect antiglobulin test. Another variant is the Rh_{null} phenotype which fails to react with any of the antibodies specific for Rh antigens. Rh_{null} red cells usually are associated with membrane defects leading to haemolytic anaemia (Sturgeon, 1970).

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* Allo-antibodies are formed in response to the introduction of a human antigen (allo-antigen) into a recipient. Auto-antibodies occur without obvious exposure to a foreign antigen, that is they are produced in their subject in response to auto-antigens.

The Kell system. In approximately 9% of Western Europeans the Kell antigen can be found in the red cells (K-positive). The K-antigen, which has several phenotypes and variants, is highly immunogenic in the 91% of the people who lack the K determining gene. Anti-Kell can cause severe transfusion reactions as well as haemolytic disease of the newborn. The Kell blood group system is very complex, and contains a large number of antigens (for example $K_p{}^a$, $K_p{}^b$, Js^a, Js^b).

Other blood group systems. Many other blood group systems have been described. In routine laboratory practice the Duffy and the Kidd systems are important because severe transfusion reactions can occur, and yet the antibodies may be difficult to detect. The Ii, Lutheran and the Xg systems as well as the so-called "private blood group antigens" are further examples of the serological complexity of the human blood groups.

LEUCOCYTE AND PLATELET ANTIGENS AND ANTIBODIES

Antibodies against antigens present on leucocytes and platelets are of clinical interest when they develop in patients after multiple blood transfusions, since they can give rise to transfusion reactions, even causing a fatal outcome (Felbo and Jensen, 1962). It is now well established that leucocytes contain antigens, the most important belonging to the HLA system. At present more than 40 HLA antigens with different antigenic specificities have been characterized showing considerable differences in their racial distribution. The HLA antigens form the major human histocompatibility system, since they have been found on a wide variety of tissues, as well as blood cells. Besides the HLA system, B lymphocyte and neutrophil specific antigens have been described (Lalezari and Radel, 1974; Winchester et al., 1975). A more detailed description of the HLA system and other white cell antigens is far beyond the scope of the present review, and the interested reader is referred to a more recent review on this subject (Bodmer, 1978).

Platelets possess most of the HLA antigens, and clinically these are the most important in antiplatelet transfusion reactions. Antibodies against platelet-specific antigenic determinants are occasionally demonstrated in mothers of infants with neonatal thrombocytopenia and in patients after multiple transfusions. These antibodies can sometimes be the cause for unexplained transfusion reactions. Sensitization to leucocyte and platelet antigens during pregnancy explains why transfusion reactions occur more frequently in women (Hattler et al., 1966; Pineda, Taswell and Brzica, 1978).

PLASMA ANTIGENS AND ANTIBODIES

Since a considerable polymorphism of some of the plasma proteins exists, it is possible that a recipient of a blood transfusion develops allo-antibodies against antigenic determinants of plasma proteins which are not present on his own proteins. Antibodies with immunoglobulin and β-lipoprotein specificities have been identified in patients after multiple blood transfusions. Occasionally febrile transfusion reactions have been attributed to incompatibility of plasma antigens. It appears that these reactions are rare and normally only of minor severity. An important exception is the presence of anti-IgA antibodies in patients with either a lack or severe deficiency of IgA. It has been calculated that the prevalence of total IgA deficiency in a normal population is between 1 in 500 and 1 in 700 (Bachmann, 1965). Thus, the chance of sensitization in these individuals by multiple transfusions is appreciable and severe anaphylactoid reactions have been observed. Antibodies against clotting factors may be found in patients with congenital coagulation disorders. Approximately 10% of haemophiliacs and patients with Christmas Disease develop inhibitors to Factor VIII or IX after transfusion of plasma or clotting factor concentrates.

TRANSFUSION REACTIONS

As indicated in table I, immunological mechanisms underlie most reactions, which can be of either the immediate or the delayed type. In anaesthetic practice the immediate transfusion reactions are most important since they occur during administration of the blood or shortly thereafter. Delayed reactions usually develop days or weeks following the transfusion. The clinical features of the immediate transfusion reaction may range from a febrile response to anaphylactic shock. They may be a result of a haemolytic reaction or sensitivity to leucocytes or platelets. Pyrexia during blood transfusion may be caused by a variety of other unidentifiable factors and the clinical decision to discontinue a blood transfusion may be difficult. Allergic reactions are considered to be mainly caused by incompatibility of plasma proteins, and the clinical picture may range from urticaria to anaphylaxis.

In anaesthetic practice a generalized bleeding tendency and the inability to improve a shock syndrome by further blood transfusion frequently represent the clinical signs of a severe immediate transfusion reaction caused by haemolysis. If a haemolytic reaction is suspected, it is essential to stop the transfusion immediately, because the severity of the reaction is proportional to the amount of incompatible blood given. Haemorrhage and renal failure are predominant features of the haemolytic transfusion reaction. Disseminated intravascular clotting (DIC) is considered to be the major pathogenic mechanism; clot-promoting material derived from the lysed red cells as well as antigen–antibody complexes are the possible triggers for DIC (Goldfinger, 1977). The diagnosis of intravascular haemolysis is invariably based on the appropriate laboratory tests, which should include a clotting screen as well as a repeat cross-match.

Haemorrhagic diathesis associated with transfusion reactions

As outlined above, haemorrhage is one of the symptoms of the acute haemolytic reaction, and may be the result of a consumption coagulopathy caused by the intravascular activation of the clotting mechanism. Thrombocytopenia, abnormal clotting screening tests and fibrin degradation products in the serum are predominant laboratory findings. However, there are other mechanisms leading to haemorrhage during blood transfusion, and an accurate laboratory diagnosis is essential for correct therapeutic measures. The anaesthesist should be aware of the fact that the most common cause of local bleeding is improper surgical haemostasis. Post-transfusion purpura is also a rare complication and occurs exclusively as a delayed transfusion reaction. Antibodies to transfused platelets may occasionally cause thrombocytopenia by interaction of the patient's own platelets with antigen–antibody complexes. Stored blood contains only trace amounts of Factor V and VIII. Thus deficiencies of these clotting factors may be encountered after massive transfusion.

Prevention of transfusion reactions

Despite the enormous increase of our knowledge about immunological mechanisms in blood transfusion and advances in laboratory techniques, the use of blood or blood products still carries a risk for the recipient. The hazards of transfusion therapy could certainly be minimized if clerical errors or incorrect identification of the patient were ruled out. Anyone involved with the preparation or administration of blood or blood products has to pay attention to minute detail. In addition, there are a few basic practices which should be observed:

(1) To avoid bacterial contamination, the blood should always be stored in controlled refrigerators with an outside temperature recorder and an alarm system.

(2) Before requesting blood, the history of past transfusions, pregnancies, previous transfusion reactions and drug intake should be given.

(3) Whenever possible, adequate time must be allowed for screening of the patient's serum for antibodies.

(4) Non-cross-matched blood should only be requested if essential. The patient's own group should preferably be used rather than blood of the group O Rh-negative. However, if there is any doubt about the patient's group or history of transfusions, O-negative blood should be used until the patient is retyped and compatible blood is available.

(5) Some antibodies are detected by complement fixation tests (for example, anti-Lewis), therefore fresh serum, in which the serum complement concentration is adequate, should be sent to the laboratory. Patients receiving regular blood transfusions should be carefully screened for antibodies at 2–3-day intervals. Some laboratory problems may be encountered if serum from patients receiving certain types of dextran is used.

It is evident that knowledge of blood group serology and the use of various blood products has made major surgical procedures easier. However, as there are still problems arising out of the extensive use of these products, they should not be used indiscriminately.

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ANAPHYLACTOID REACTIONS TO I.V. SUBSTANCES

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Although i.v. therapy offers numerous advantages to the clinician, a wide variety of complications of i.v. therapy exists (Jaeger and Rubin, 1970; D'Arcy and Thomson, 1974; Woods and Marston, 1977). It is important to realize that anaphylactoid or "hypersensitivity" reactions occupy only a small part of this range of complications. Nevertheless, the majority of reactions can be avoided, for example microbial contamination of infusion sets, or the interactions of solutions of unsuitable pH or inorganic salt content, and it is the anaphylactoid response which is of increasing interest and importance since there are at present no ways of satisfactorily predicting such reactions.

I have purposely refrained from the term "allergic" to describe these reactions since that automatically implies an immune-mediated response. The clinical manifestations, cutaneous (for example flushing or urticaria), pulmonary (such as bronchospasm) and cardiovascular (such as hypotension) do indeed resemble those produced by the immediate, immune-mediated, hypersensitivity response since the chemical mediators of such reactions, predominantly histamine, are identical. Nevertheless, in the absence of laboratory tests to confirm the mechanism, clinical manifestations alone cannot be used to distinguish between antibody-mediated reactions, complement-mediated reactions and reactions occurring by the release of histamine from mast cells by the direct action of the injected substance. On the basis of clinical observation alone, hypersensitivity-type reactions are best described as anaphylactoid, the term anaphylactic or allergic being reserved for those reactions in which evidence for definite antibody involvement exists. This terminology was accepted at the Symposium on Adverse Response held in Sheffield, 1978 (Watkins and Clarke, 1978). A second descriptive term, "histaminoid", may be used to describe chemical reactions restricted to cutaneous phenomena such as flushing or urticaria.

HYPERSENSITIVITY REACTIONS

Before proceeding further with the action of specific i.v. substances it is worth summarizing the four major reaction mechanisms which comprise the hypersensitivity response scheme. These are designated Types I to IV and are admirably described in detail in a number of textbooks (Barrett, 1977; Roitt, 1977). The Type I reaction most resembles that exhibited by patients showing anaphylactoid response to i.v. substances since it is, by definition, immediate. This immunological reaction is for the most part restricted to a genetically prone individual who produces a specific type of antibody, termed a reagin (generally IgE), in response to antigens or allergens which are well tolerated by the population as a whole. In order to produce anaphylaxis these unfortunate patients still require *previous antigenic challenge* in order to achieve a passive sensitization state. If we are considering allergies which result from natural oral or respiratory immunizations then it is not usually necessary to speculate on the mechanism but only on the specific allergen, but reactions which occur to compounds that the individual has never seen before are most unlikely to be Type I hypersensitivity reactions. Unlikely, but not impossible, since some administered i.v. substances may closely resemble natural antigens such as bacterial proteins and polysaccharides, so that immunological cross-reactions may occur.

Once produced, the reaginic antibodies adhere to mast cells. Subsequent antigen challenge causes a physico-chemical reaction upon the surface of the cell which leads to degranulation. The resulting histamine release causes either local cutaneous phenomena or systemic anaphylaxis.

The reaginic antibodies are for the most part the IgE class of immunoglobulins. However, IgG reagins are also known (Parish, 1970; Berrens, Koers and Bruynzeel, 1977); these, unlike IgE, may involve complement proteins for the release of histamine. The patient with high IgE concentrations (>400 iu ml^{-1}) in the plasma is frequently described as atopic: such concentrations are frequently observed in the patient with atopic asthma and in well-defined allergy

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states. It must be observed, however, that this is still a somewhat crude classification, since we should be considering *specific* IgE antibodies and normal or even decreased concentrations of plasma total IgE may conceal important allergies. Finally, it is the cell-bound IgE which is of importance in the Type I reaction: the parallelism between humoral antibody and cell-bound antibody may not hold for certain individuals.

Type II reactions also are described as antibody-dependent cytotoxic hypersensitivity responses. Again, the patient requires previous antigenic challenge to produce antibodies, but the antigens in this case are present on the surface of either host or foreign cells. Combination of antibody with cellular antigens encourages demise of that cell either by phagocytosis or by activation of the full classical complement pathway up to C8 and C9, producing lysis. Adverse reactions invoking this type of mechanism include transfusion reaction, rhesus incompatibility and long-standing organ transplants. Autoimmune conditions such as Hashimoto's thyroiditis and Goodpasture's syndrome proceed through this mechanism and so may certain types of drug reaction. In the latter, drugs with simple molecular structure may be bound to cell membranes, thus undergoing conversion from haptens to full antigens. The resulting complex may then evoke autoantibodies, for example haemolytic anaemias to phenacetin. However, the majority of small-molecule drugs are more likely to couple to plasma proteins, giving rise to complex-mediated (Type III) reactions.

The formation of *excessive* amounts of soluble complexes of antigen and antibody may fix complement, releasing anaphylatoxins which cause histamine release, vascular permeability changes and an influx of polymorphs which in turn release further factors contributing to the inflammatory response. Two types of complexes may be found, those with *antibody* excess and those with *antigen* excess. In antibody excess (Arthus-type) the complexes are rapidly precipitated and tend to be localized in the site of antigen introduction. This type of reaction is illustrated in figure 1—an anaphylactic response to thiopentone. This particular reaction, however, also produced a systemic response resulting in hypotension.

The final hypersensitivity scheme, Type IV, cell-mediated (delayed), is encountered in allergic reactions to bacteria and the like and in the rejection of transplanted tissues. Comparable reactions to soluble proteins are obtained when sensitization is induced by incorporation of the protein into Freund's adjuvant. This raises interesting possibilities regarding the use of detergents or solubilizers for several anaesthetic drugs (for example propanidid, Althesin, etomidate). The effector mechanism is essentially the T lymphocyte.

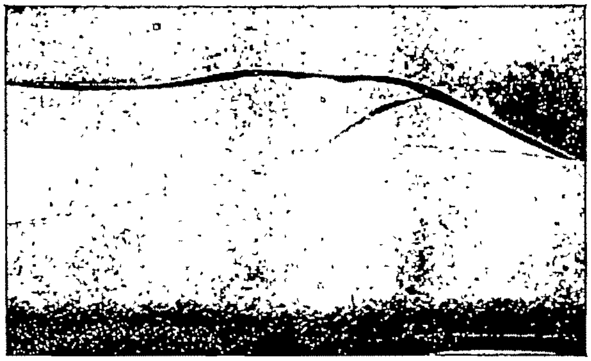

FIG. 1. Fixed drug reactions on the arm of a patient who exhibited a marked anaphylactoid reaction to thiopentone. The flared areas correspond to the precipitation of specific antibody–drug complexes on the sites of previous venipunctures and not to the site of administration of the anaesthetic (dorsum of hand). The patient had received a previous exposure to the drug uneventfully. Photograph by kind permission of Dr P. Latto, Anaesthetic Department, University Hospital of Wales, Cardiff.

It should be clear to the reader that these hypersensitivity reactions do not represent abnormal mechanisms. In themselves they are extremely important in the control of numerous disease processes. It is the *magnitude* of their involvement in a particular reaction which defines their abnormality. Perhaps not so obvious is the fact that few, if any, hypersensitivity reactions involve specifically one particular mechanism. A Type I reaction may act as a trigger for a Type III, the influence of the former being hidden by the magnitude of the secondary response. Likewise, an apparently insignificant immune reaction may trigger complement non-classically, producing large quantities of anaphylatoxin and systemic anaphylaxis.

Complement

Only the Type I and Type IV reactions may proceed directly without the involvement of the complex system of complement proteins. These proteins, which comprise nine major components, represent nearly 10% of the globulins in the human so it is not surprising that complement participates in several important biological functions (Schur and Austen, 1968; Ruddy, Gigli and Austen, 1972).

Traditionally, the combination of antigen and antibody gives rise to a cascade activation of complements C1 to C9, somewhat analogous to clotting mechanisms. The scission products of complement activation have specific biological functions. The products C3a and C5a are known as anaphylatoxins. Not only are they responsible for histamine release, but they also intrude into the blood clotting system, causing aggregation of platelets. Complements C3 and C4 exist in plasma in relatively high concentration, C3 in excess of 1 g $litre^{-1}$ and C4 perhaps 0.5 g $litre^{-1}$. They are easily measurable by conventional immunochemical techniques (Mancini, Carbonara and Heremans, 1965). Complement C3 is of particular interest to the immunologist, since it can be directly activated without a specific antigen–antibody reaction; this is the basis of the so-called alternate pathway mechanism. Like most potentially "active" plasma proteins, complement C3 is held in a dynamic state by specific protease inhibitors:

$$C3 \longrightarrow C3a\,(\text{anaphylatoxin}) + \overline{C3b}$$

These normally inactivate $\overline{C3b}$, producing a large inactive molecule C3c, while the tissue can comfortably absorb the small amount of histamine produced by the anaphylatoxin. However, if by blocking of the C3b inactivator, or by sudden excessive breakdown of C3 itself, the highly active $\overline{C3b}$ molecule exceeds some predetermined threshold, then a feedback mechanism takes place through C3 proactivator, activating more and more C3 with subsequent massive histamine release. Some i.v. substances, such as Althesin and propanidid, have a particular tendency to this type of non-immunological activation: with others such as dextrans, alternate pathway activation is uncommon. In the laboratory, complement C3 conversion can be readily demonstrated in sequential samples of patients' plasma taken after reaction (Watkins, Udnoon et al., 1976), either by conventional single-dimension immunoelectrophoresis (fig. 2) or by the two-dimensional Laurell technique (Laurell, 1965) which display C3 and its reaction product C3c in the form of peaks of precipitin, the relative areas indicating the degree of conversion (fig. 3).

Chemical mediators of anaphylaxis

Several important pharmacologically active compounds are discharged from cells during anaphylaxis. Histamine is the most important of these and the only one proven to be essential to the anaphylactic response (Lorenz et al., 1972, 1976, 1977). The other substances of putative significance are serotonin, bradykinin and other kinins, slow reacting substance-anaphylaxis (SRS-A), and prostaglandins. The function of the last may well be the modulation of histamine release (Engineer et al., 1978), since prostaglandins are known to cause granule reabsorption by mast cells. It is worth noting that the systemic anaphylactic response not only shows striking variation according to the species studied, but also varies in its intensity in different individuals. This is attributed to species differences in susceptibility of different tissues (the shock organ), to histamine liberated in the course of the reaction, and also to variations in the individual distribution of the sensitized mast cells.

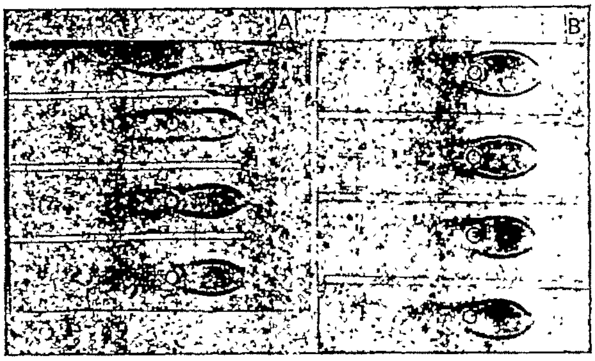

FIG. 2. Conventional agar immunoelectrophoresis of sequential plasma samples taken over 24 h following anaesthesia with Althesin. Protein migration is towards the left of the photographs, the "troughs" contain anti-C3 antiserum. (A) Samples from a patient who exhibited a marked anaphylactoid response. The first sample (1 h) shows marked C3 conversion (>50%) with the C3C conversion product very evident. Conversion products are gradually removed over 24 h (sample 4). (B) C3 electrophoresis patterns from a patient who had an uneventful induction of anaesthesia. The time sequences of the samples are comparable to samples 1–4 of (A). C3 conversion is minimal.

FREQUENCY OF ANAPHYLACTOID REACTIONS

The definition of frequency implies that the adverse response can be quantitated in some simple and universally adopted manner. This is not so, and it is evident from table I that, particularly for Althesin, much of the variability must lie in what is regarded as a significant anaphylactoid response by the observer. Laboratory investigations (Lorenz, 1975; Watkins, Clark et al., 1976) indicate that subclinical anaphylactoid reactions occur in many people following the administration of i.v. hypnotic agents. These reactions presumably do not exceed a genetically

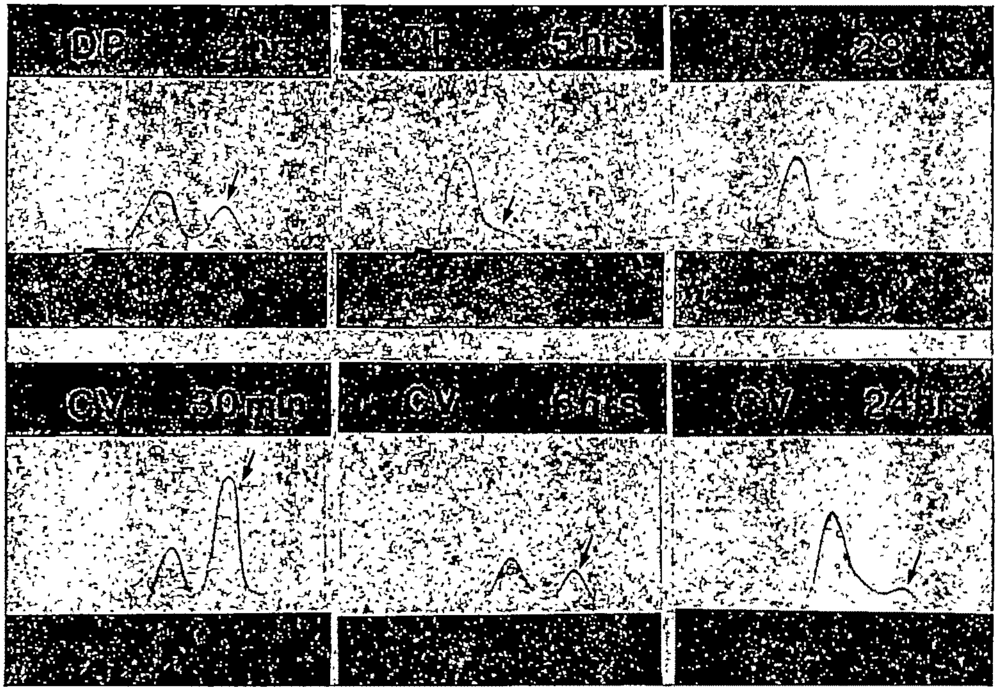

FIG. 3. Laurell immunoelectrophoresis patterns of C3 components in plasma taken from patients D. P. and C. V. showing anaphylactoid response after induction with Althesin for identical minor surgical procedures. Sample times after injection are indicated. Note the initial high degree of conversion (twin peaks): the C3c inactive products are indicated by the arrows. The surgical procedure had to be abandoned in the case of patient C. V. in whom significant conversion persisted for 24 h. Patient D. P. exhibited a lower degree of conversion and it was possible to continue surgery (reproduced by permission from Watkins, Udnoon and Taussig (1978).

TABLE I. *Reported frequency of anaphylactoid response to i.v. hypnotics (reproduced by permission from Clarke, Fee and Dundee* (1978))

Propanidid		
Dannemann and Lubke (1970)	1 in	750
Kay (1972)	1 in	1 700
Doenicke (1974)	1 in	540
Methohexitone		
Driggs and O'Day (1972)	1 in	7 000
Althesin		
Clarke et al. (1975)	1 in	11 000
Watt (1975)	1 in	900
Fisher (1976)	1 in	900
Evans and Keogh (1977)	1 in	930
Thiopentone		
Evans and Keogh (1977)	1 in	14 000

defined threshold for the individual. Measurement of histamine release is theoretically ideal for defining reactions, but the experimental requirements are totally unsuited for clinically severe cases under theatre conditions. In trying to assess the predominant reaction mechanisms from the literature, the absence of a measure of reaction severity presents the first stumbling block.

Intravenous hypnotics

The work of Clarke, Dundee and their colleagues (Clarke et al., 1975) has clearly indicated that clinical features include skin changes, hypotension, bronchospasm and abdominal symptoms, in that order of frequency. Their work demonstrates the fallacy of adverse response reporting in the absence of a measure of severity. In spite of some 90 reactions to Althesin reported in the literature only one death has occurred, whereas there have been six deaths reported in 45 reactions following thiopentone. The data can be interpreted to indicate that although the patient is more likely to have a reaction to Althesin than to thiopentone, any reaction to the former is unlikely to be fatal. Fisher (1977a) considers a general frequency of 1 in 5000 for i.v. hypnotics with increasing frequency attributed to cross-sensitivity and the greater number of drugs used per anaesthetic (Fisher, 1975). Muscle relaxants, particularly suxamethonium and gallamine, also appear to be frequently involved in anaphylactoid response (Fisher, 1975). For several years the relaxant tubocurarine has been known to release histamine (Comroe and Dripps, 1946) and it has also been suggested that this drug causes bronchospasm (Bennett et al., 1970). There is little doubt that some reported reactions to i.v. hypnotic agents involve the muscle relaxant, but no valid figures exist for the frequency of reactions to these drugs.

Contrast media

Adverse reactions to intravascular radiological contrast media, essentially tri-iodo substituted derivatives of benzoic acid, are probably more frequent than with any other i.v. substance. The large dose (perhaps 140 g injected intravascularly within 30 min) gives rise to adverse reactions predominantly as a result of the osmolarity of the injected solution (×5 to ×8 plasma). Mild reactions occur in 1 in 2000 administrations, severe 1 in 20 000, and fatal 1 in 40 000 administrations (Witten, 1975).

Plasma substitutes

Modern plasma substitutes include plasma protein preparations, modified gelatins, dextrans and starches. Anaphylactoid manifestations resemble those of the i.v. hypnotics, with cutaneous effects, bronchospasm and hypotension as predominant features. In spite of a large number of case reports published during the past decade the frequency of reactions to plasma substitutes has been uncertain (Ring et al., 1975). Recent work by Ring and Messmer (1977) suggested a frequency of anaphylactoid reactions of 1 in 10 000 for plasma protein preparations, 1 in 1000 for gelatine, 3 in 10 000 for dextran and 8 in 10 000 for hydroxyethyl starch. However, Lorenz and Doenicke (personal communication) suggest that the total number of reactions is considerably greater.

MECHANISMS AND PREDISPOSING FACTORS

This laboratory has previously suggested simple tests (Watkins, Udnoon et al., 1976) involving measurement of the consumption and conversion of complement C3 and C4 and immunoglobulin IgE on serial samples of the patient's plasma taken over the 24 h following reaction. These tests, considered *in relation to* the clinical features of the case, afford a useful tool in distinguishing the mechanism of the adverse response. If such tests are not undertaken then investigations into predisposing factors will be of limited value. Based on our experiences, we suggest that four basic mechanisms are involved, although more than one mechanism may be involved in a given reaction. These reaction mechanisms may be conveniently summarized as follows:

(1) *Type I hypersensitivity response.* These require previous exposure and involve IgE antibodies. There is direct histamine release from mast cells *without* the involvement of complement.

(2) *Immune reactions.* The class of immunoglobulin involved may be in doubt, but histamine release occurs by the classical complement pathway. Immunochemically, serial samples show complement C4 and C3 consumption with varying degrees of C3 conversion, generally less than 30%.

(3) *Alternate pathway activation of C3.* These involve direct activation of C3 and consequently high levels of C3 conversion may be observed in plasma samples. Complement C4 shows no significant consumption or conversion in the reaction. This group appears to contain both individuals apparently sensitized by previous exposure to the substance and first time responders.

(4) *Pharmacological or chemical release of histamine.* The injected substance causes histamine release directly from the mast cell without antibody or complement involvement. This may reflect drug concentration, speed of injection, the distribution of mast cells in the vascular system, or a combination of these.

Table II shows the analysis of reactions reported to this laboratory between 1974 and 1977, predominantly to Althesin and thiopentone. Although there are no *clinical* differences in the adverse responses to these drugs (Garrett, 1978) it is quite clear that two very different mechanisms predominate. Althesin reactions generally involve excessive (alternate pathway) activation of complement C3, leading to histamine release, and are not reagin-antibody mediated. In contrast, barbiturate reactions generally represent immediate immune-mediated, hypersensitivity reactions. The latter, of course, will have required previous exposure to the agent in order to produce immune sensitization. This is in contrast to complement-mediated reactions, which can occur on first exposure without previous sensitization. We would therefore expect atopic individuals to be at higher risk than the normal population with substances tending to produce antibody response. This is well illustrated in table III, a survey by Clarke, Fee and

TABLE II. *Analysis of reactions reported between* 1974 *and* 1977

	Cases reported	Mechanism analysis possible	Complement involved		IgE involved	Probably pharmacological
			Classical	Alternate		
1974						
Althesin	19	5	1	4	2/5	0/5
Thiopentone	1	0	0	0	0	0
Methohexitone	1	1	0	1	1/1	0/1
1975						
Althesin	16	7	3	4	2/7	0/7
Propanidid	1	0	0	0	0	0
Thiopentone	1	1	0	0	0/1	0/1
1976						
Althesin	15	12	4	6	1/10	2/12
Propanidid	2	2	0	2	0/2	0/2
Thiopentone	2	2	1	1	2/2	0/2
1977						
Althesin	12	11	1	5	0/11	5/11
Thiopentone	6	5	3	1	4/5	0/5
Thiopentone/dextran*	2	1	0	1	0/1	0/1
Dextran	2	1	0	1	0/1	0/1

* Reaction time relative to drug administration suggests these were dextran reactions.

TABLE III. *Percentage frequency of a history of atopy, allergies and previous anaesthesia (from Clarke, Fee and Dundee,* 1978)

	Number of surgical patients	Patients reacting (Clarke et al., 1975)
Number questioned	5500	86
Eczema, hay fever or asthma	9	14
Drug or food allergies	14	19
Previous anaesthesia	66	61
Same anaesthetic previously	0	47

Dundee (1978) of allergy and hypersensitivity conditions in a group of random surgical patients and in a group of "adverse responders". It is clear that previous exposure to the agent is an important factor predisposing to anaphylactoid response and indicates that the same drugs should not be used repeatedly in patients with known atopy. The necessity for laboratory investigations is now more obvious because there is little point in excluding a patient from say, Althesin, if in fact the muscle relaxant is the causative factor.

In theory, since many reactions to Althesin occur on first exposure by complement C3 activation, there seems little point in excluding this drug from atopic patients. However, Althesin is a steroid drug and the action of steroids on the immune system overall are complex and not fully understood. We find it surprising that antibodies to the Althesin formulation do appear to be produced and we have previously speculated on the role of the surfactant, Cremophor EL, as an adjuvant in this respect.

Complement C3 activation appears to be a frequent feature of the anaphylactoid response to i.v. hypnotic agents and to radio-contrast media (Heideman, Jacobsson and Lindholm, 1976; Lang, Lasser and Kolb, 1976), but not to plasma substitutes. The latter may predominantly involve "aggregate anaphylaxis" (Becker and Austen, 1976). However, it is often far from clear as to what constitutes direct complement activation and what constitutes "feedback" following an initial immune-mediated event. It is becoming evident that some individuals have an inherent (genetic) instability of complement C3 while in others the instability may arise as a result of underlying immunopathological conditions involving circulatory immune complexes (Type III reaction). Such conditions may include auto-immune disease such as systemic lupus erythematosis (SLE) and rheumatoid arthritis or even chronic infection (Watkins, Ward and Appleyard, 1977). It is worth noting that these conditions do not presuppose antibodies directed against the drug or drug complex, but merely "immune complexes". Such reactions can be readily demonstrated *in vitro* using either heat-aggregated IgG preparations or IgG anti-albumin–albumin complexes to convert plasma C3. Thus we may have the curious situation in which the patient may have reacted against the drug rather than the drug reacting specifically with the patient. Such reactions may be triggered non-specifically by any substance which exacerbates an underlying primary (genetic) or secondary (induced) immunopathological condition and may explain why the patient later reacts adversely to a drug totally different from that which was implicated in the first reaction (Watkins, Padfield and Alderson, 1978).

A further, apparently genetic, factor involves complement C2 (Ruddy et al., 1970). Activation of this second component of complement gives rise to angioeurotic oedema without C3 intervention.

On the subject of possible genetic effects and response to i.v. hypnotics, there is a curious situation with regard to certain patients receiving more than one exposure to Althesin. In addition to patients in whom reaginic antibodies appear to be involved, there is a second group in whom anaphylactoid response follows a second exposure to Althesin, 1–4 weeks after the first administration. Preliminary studies show that either the patients themselves or their families have increased IgD concentrations, with one or more of the family displaying atopic concentrations of IgE (Watkins, Allen and Ward, 1978). IgD is a lymphocyte receptor and may have memory characteristics for short-term response (Rowe et al., 1973; Bargellesi et al., 1978). An analogous situation in the miniature pig model has been reported in detail by Glen and others (1978). Here, although Cremophor EL also elicited a short-term response, alphaxalone itself was definitely implicated (reported at the Sheffield Symposium, 1978). Perhaps we have here a hybrid Type I/Type IV reaction.

Mechanisms specific to plasma substitutes

Unlike the hypnotic and muscle relaxant drugs which are haptenic at best, plasma substitutes are potentially antigenic compounds in their own right. Despite the clinical similarity of adverse reactions produced both by the hypnotics and by plasma substitutes, it would not be surprising if the predominant mechanism of response differed. Richter and his colleagues (1978) produced convincing evidence for the involvement of soluble aggregates or immune complexes in patients reacting to all types of plasma substitute. Among plasma protein solutions human serum albumin (HSA) is most widely employed. Here aggregates may form as a result of polymerization upon storage (Ring, 1976) and these may give rise to "early" reactions. Late reactions in patients, 3 or more days after administration may represent the immunological consequences of the genetic polymorphism of albumin (Weitkamp et al., 1973). Dextrans and gelatins may react specifically with antibodies or non-specifically with euglobulins present in the plasma of many patients (Richter, Hedin and Ring, 1977). In the case of the dextrans, preformed antibodies (Hedin, Richter and Ring, 1976) may exist from the body's experience of cross-reacting bacterial polysaccharides. Despite their apparent involvement in adverse clinical reactions, the activation pathway of these complexes remains far from clear although complement C3 activation does not appear to be an important factor. This again may reflect the problem of not reporting severity of reaction. In man, most plasma substitute reactions to dextrans, gelatins and starches involve urticaria and gut reactions rather than vascular changes; it is possible that these represent stimulation of the axon reflex. In contrast, the author has seen excessive C3 activation in two fatal reactions to dextran so that the latter may represent a fortunately rare mechanism for response to dextrans (see also Johnson and Laurell, 1974). In man, plasma histamine release to plasma expanders is relatively uncommon (Lorenz et al., 1973, 1975).

Factors predisposing to anaphylactoid response

In summary, the principal factors predisposing to anaphylactoid response include (a) genetic features such as atopy (IgE), possibly increased IgD and primary complement anomalies; (b) frequency of exposure to the agents, with anomalous behaviour to Althesin; (c) underlying immune or auto-immune processes leading to complement C3 instability and probably activation of other secondary immune effectors such as prostaglandins; (d) pharmacological effects and (e) stress. The last, we have not considered previously, but there is no doubt that anaesthetic and surgical trauma combine to produce marked alterations in hormone concentrations in the patient, mediated through various centres of the brain. This gives rise to specific changes in protein chemistry, cell metabolism and both the cellular and the humoral "limbs" of specific immune response.

MANAGEMENT OF THE ANAPHYLACTOID RESPONSE

Prevention

Active prevention may lie in two types of drug, disodium cromoglycate and H_1 and H_2 receptor antagonists. Disodium cromoglycate has not been sufficiently studied in pre-anaesthetic medication (Watkins, Clark et al., 1976), but it may be particularly effective in preventing bronchospasm in susceptible individuals (see review by Altounyan, 1969; Orr, 1975). Unfortunately, it is of no value in treatment of an established reaction. Since histamine release is the cause of all the tissue-damaging and life-threatening reactions, pretreatment with anti-histamine is a logical measure, particularly in atopic patients. However, both H_1 and H_2 actions should probably be antagonized (Lorenz et al., 1977) using a combination of drugs (for example promethazine with cimetidine). The potential toxicity of steroids make their use for prophylactic therapy undesirable (Munroe-Ford, 1977).

Treatment

A common manifestation of anaphylactic reaction is hypotension accompanied by extravasation of fluid into extracellular tissues (Fisher, 1977a). This is usually mediated by histamine which induces peripheral vasodilatation and venous pooling, although other plasma factors may produce similar effects. Clearly, the lost fluid should be restored, preferably using a colloid plasma expander. Fluid should be transfused rapidly up to a volume of 1–2 litre (Fisher, 1977a), but the volume must be continuously monitored by the central venous pressure. In contrast to i.v. hypnotic agents and muscle relaxants, anaphylactic reactions to plasma substitutes are relatively slow in onset. In the event of reaction the infusion should preferably be changed to HSA, which is the colloid least likely to cause trouble.

In acute hypotension the most favoured drug is adrenaline (Kelly and Patterson, 1974). Isoprenaline is also effective, but may be undesirable because of pre-existing tachycardia and in this case α-adrenergic stimulators such as metaraminol would seem to be specifically indicated. However, α-adrenergic and cholinergic drugs reduce the cell content of cyclic AMP and may enhance histamine release. On balance, a drug which has a direct effect on smooth muscle would appear to be indicated, such as angiotension amide (Whitwam, 1978).

Bronchospasm is the most life-threatening feature of anaphylactoid response (Fisher, 1977b) and can only be treated by tracheal intubation and administration of oxygen, adrenaline and aminophylline.

CONCLUSIONS

Relatively few anaphylactoid reactions to i.v. substances are antibody-mediated. Many involve secondary effectors of the immune response directly. Although it is possible to define at least four basic mechanisms, it is obvious that these overlap and more than one may occur in any given reaction. It is not possible to assign a particular reaction mechanism to a particular i.v. substance, although most drugs have a preferred mode of response. Thus, reactions to thiopentone generally require multiple exposure to that drug and frequently represent Type I hypersensitivity reactions. In contrast, some 40% of Althesin reactions involve first exposure to the drug and result from complement activation.

True anaphylaxis is dangerous, particularly with "long-lived" drugs like the barbiturate hypnotics and this is probably the reason why the less frequent reactions to thiopentone cause more deaths than those to Althesin. Radiological contrast media have probably the highest potential risk with a fatality rate of 1 in 40 000 patients injected: here complement C3 activation appears to be the harmful factor. The position is further complicated by the way in which individual patients respond to a specific substance. This may be at complete variance with its expected adverse response mode and presumably reflects genetic factors influencing responsiveness.

Although we cannot pinpoint the patient at risk we can at least take simple and practical steps to reduce the possibility of response in high-risk patients.

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PROCEEDINGS OF THE ANAESTHETIC RESEARCH SOCIETY

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RESPIRATORY EFFECTS OF MEPTAZINOL (WYETH): A NEW POTENT ANALGESIC

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Meptazinol is a new hexahydroazepine analgesic which has been shown to produce significant pain relief in doses of approximately 60 mg per 70 kg i.m. in patients recovering from abdominal surgery (Paymaster, 1976).

Meptazinol 60 mg per 70 kg i.m. and morphine 10 mg per 70 kg i.m. were compared with a placebo in three male volunteers. A double-blind crossover technique was used. A minimum of 48 h was allowed to elapse between the administration of each drug and the placebo. The respiratory effects were evaluated at intervals following injection, by the following tests:

(i) The slope of the ventilation/$P\mathrm{CO}_2$ plot ($\dot{V}/P\mathrm{CO}_2$) was determined by the rebreathing method of Read (1967).

(ii) The slope of the mouth occlusion pressure ($P_{0\cdot1}/P\mathrm{CO}_2$) plot (Whitelaw, 1975) was determined simultaneously with (i).

(iii) The end-tidal carbon dioxide partial pressure ($P\mathrm{E}'_{\mathrm{CO}_2}$) was measured during breathing at rest.

(iv) An inspiratory load of 8 kPa litre^{-1} s was added and the resulting change in $P\mathrm{E}'_{\mathrm{CO}_2}$ was measured.

Tests (i) and (ii) were performed in duplicate and all results were compared with the mean placebo values. The respiratory effects were recorded over a period of 6 h.

Following injection of morphine there was a consistent and significant ($P < 0.005$) depression of the $\dot{V}/P\mathrm{CO}_2$ slope (mean 58% of control, SD 5.6%). Meptazinol, however, produced no apparent change in slope (mean 91%; SD 4.5%). $P_{0\cdot1}/P\mathrm{CO}_2$ slopes also showed depression following morphine (mean 57%; SD 42%), while there was little apparent change following meptazinol (mean 88%, SD 20%). Following injection of morphine there was a consistent and significant ($P < 0.005$) increase in $P\mathrm{E}'_{\mathrm{CO}_2}$ during breathing at rest (0.45 kPa; SD 0.05 kPa). A smaller increase which was not statistically significant occurred following injection of meptazinol (mean 0.21 kPa; SD 0.27 kPa). The increase in $P\mathrm{E}'_{\mathrm{CO}_2}$ which followed application of the load was not affected appreciably by either morphine or meptazinol.

The results of this study suggest that meptazinol produces less respiratory depression than morphine.

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MEASURING AGREEMENT BETWEEN ANAESTHETISTS

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Anaesthetists are often regarded as individualists who adopt differing views about the condition of patients and the most appropriate anaesthetic techniques. During an investigation into the preoperative judgements of anaesthetists, we took the opportunity to measure the overall agreement in a group of 10 anaesthetists and also to measure the agreement between pairs of anaesthetists.

Three levels of preoperative information were collected from 200 patients: level A—details of past medical history, general health and functional ability; level B—the physical examination; level C—special investigations. Ten consultant anaesthetists were asked to make various judgements on this information, from a sub-sample of 100 of these patients, regarding the need for (i) further investigations, (ii) special care or monitoring, (iii) avoidance of certain anaesthetic agents or techniques and (iv) the fitness of the patient using an arbitrary scale (1 = perfectly fit, 4 = least fit). The extent of agreement was measured using the Kappa statistics (Cohen, 1960, 1968) which expresses the proportion of agreement corrected for chance. It varies from +1.0 for perfect agreement, 0 for chance, to −1.0 for complete disagreement.

Table I presents the overall agreement between anaesthetists for the different judgements. Anaesthetists agree best over the decision that a patient is perfectly fit. They also

TABLE I. *Kappa values for overall agreement*

	Level of information		
	A	A+B	A+B+C
Further investigations needed	0.512	0.492	0.181*
Special care required	0.375	0.343	0.396
Avoid certain anaesthetics	0.104†	0.109†	0.159*
Treatment required	0.226†	0.266†	0.222*
Fitness categories 1	0.592	0.599	0.626
2	0.255	0.246	0.280
3	0.223	0.222	0.233
4	0.264	0.237	0.173
Overall fitness agreement	0.366	0.360	0.382

Significance levels: † not significant; * $P < 0.05$; otherwise $P < 0.001$.

agree well on the need for further investigation, although this agreement is weaker at level A+B+C. There is also agreement on the need for special care, although agreement on the avoidance of certain anaesthetic agents or techniques does not exceed chance (at the A and A+B levels). In addition, this technique allows agreement between pairs of anaesthetists to be examined so that pairs who agree closely or poorly can be discovered. This has practical implications for the preoperative assessment of each other's patients.

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INTERACTION OF PROPANIDID AND SUXAMETHONIUM WITH HUMAN PLASMA CHOLINESTERASE *IN VITRO*

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Pseudocholinesterase has been cited by several workers (Doenicke et al., 1968; Holst-Larsen, 1976) as the key enzyme in the *in vivo* metabolism of both propanidid and suxamethonium. This enzyme has been shown to be influenced by pancuronium and ketamine (Schuh, 1975). It is well known also that neuromuscular blockade induced by suxamethonium is prolonged if propanidid is used as the induction agent. The present study sought to elucidate the molecular mechanism underlying this phenomenon.

Pooled human plasma cholinesterase activity was assayed *in vitro* using a colorimetric method (Schuh, 1975) at 25 °C, and a pH of 7.20 using butyrylthiocholine as substrate. A propanidid concentration of 2.0 mmol litre^{-1} caused a 50% inhibition of enzyme activity *in vitro*. In contrast, a concentration of suxamethonium 4.4 mmol litre^{-1} was required to produce the same degree of inhibition.

The effects on the enzyme of propanidid, suxamethonium and a combination of the two agents are summarized in table I. Propanidid is more potent an inhibitor than suxamethonium and at a concentration of 4.04×10^{-3} mol litre^{-1} causes a 10-fold increase in K_m as compared with uninhibited enzyme. Dilution of propanidid altered V_{max} but a Lineweaver–Burk plot revealed that K_m remained unaltered over a range of the inhibitor concentrations. In the presence of suxamethonium 12.4 mmol litre^{-1}, K_m of the enzyme was increased five-fold compared with uninhibited enzyme. K_m was unaltered over a range of suxamethonium concentrations. These experiments indicate that the mechanism of inhibition of the enzyme is of the non-competitive type and that neither propanidid nor suxamethonium acts as alternative substrate for the enzyme. This is in contrast to the work of Doenicke and others (1968) and Schuh (1975), whose experiments suggest that pseudocholinesterase is involved in the metabolism of these agents.

Table I. *Values for K_m and V_{max}/K_m obtained using propanidid and suxamethonium both separately and in combination at the stated concentrations*

K_m (mol litre^{-1})	V_{max}/K_m	Inhibitor	Concentration (mol litre^{-1})
6.6×10^{-4}	3.2×10^{3}	Propanidid	4.04×10^{-3}
1.6×10^{-4}	12.5×10^{3}	Suxamethonium	12.4×10^{-3}
3.3×10^{-4}	6.0×10^{3}	Propanidid and suxamethonium	2.02×10^{-3} 6.02×10^{-3}
8.3×10^{-5}	2.4×10^{4}	Control—no inhibitor	—

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EFFECTS OF ANAESTHETICS AND HELIUM PRESSURE ON ACETYLCHOLINE RELEASE

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Using a superfusion technique inside a high pressure chamber, spontaneous release of acetylcholine by the guineapig ileum was studied, to determine the contribution of changes in neurotransmitter release to the actions of anaesthetics and to the effects of helium pressure.

The anaesthetic agents studied were nitrous oxide, nitrogen, argon, sulphur hexafluoride, carbon tetrafluoride, urethane and octanol. All of these except octanol and urethane caused considerable increases in release of acetylcholine at concentrations corresponding to those found during light anaesthesia. Octanol did not cause any significant changes while urethane decreased the amount of acetylcholine released. These changes were not altered by the application of helium pressure at 130 atm. This pressure of helium has been shown to reverse completely anaesthesia *in vivo* (Lever et al., 1971).

Helium pressure alone, at 130 atm, produced a small increase in resting release of acetylcholine. The presence of this effect in tetrodotoxin-treated tissues suggests that pressure affects the neurotransmitter release mechanism as well as conduction of action potentials.

Further studies on the effects of the anaesthetic agents showed that the proportionate increase in output produced by nitrogen was not reduced by tetrodotoxin treatment, but was reduced considerably by removal of calcium. The changes therefore were not confined to effects on action potentials and involved a calcium-dependent component of neurotransmitter release.

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THE POSSIBLE ROLE OF IMMUNOGLOBULIN IgD IN THE ANAPHYLACTOID RESPONSE TO ALTHESIN

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Reactions to the i.v. barbiturate drugs are infrequent and are usually genuine hypersensitivity responses. In contrast, reactions to Althesin occur more frequently and appear to be mediated predominantly by direct complement (C3) activation (Watkins, Ward and Appleyard, 1977). Nevertheless, a number of Althesin reactions do appear to be immune-mediated. These include a group producing marked anaphylactoid reactions when Althesin is re-administered at an interval of 1–4 weeks after an initial exposure. It is possible, but unlikely, that conventional antibody response could occur in such a time interval, particularly with a steroid drug, and we have speculated on the possibility of a short term "memory" involving lymphocyte receptors. This view is strengthened by the discovery of a similar reaction to Althesin in minipigs (Glen et al., 1978). In this animal a second exposure within 2 weeks produces a marked anaphylactoid reaction which is greatly diminished or is absent when the second exposure is administered either less than 1 week or more than 2 weeks after the "sensitizing" exposure. It appeared possible that immunoglobulin IgD is involved in the human, since it is known to be present on an unexpectedly high proportion of circulating B lymphocytes (Rowe et al., 1973).

Plasma IgD was measured by single radial immunodiffusion in agar using commercial standards and antiserum (Hoechst, U.K.). IgE was estimated by solid-phase radioimmunoassay (Pharmacia Diagnostics.) Plasma IgD and IgE concentrations in some patients who exhibited anaphylactoid reactions to Althesin are shown in table I.

TABLE I. *Plasma concentrations of IgD and IgE (iu ml^{-1}) in patients exhibiting anaphylactoid reactions to Althesin*

Mechanism	Time interval between exposures	IgE	IgD
Complement mediated ($n = 6$)	First exposure	Mean = 84 Range = 19–260	Mean = 11 Range = 0–25
Memory ($n = 3$)	3 weeks	760	115
	1 week	16	150
	2 weeks	> 1000	18
Normal adult population	—	Median = 83 95th centile = 200	Median = 15 95th centile = 85

Patients showing complement-mediated reactions have IgD and IgE concentrations similar to those of the normal population. In contrast, of three patients who exhibited a reaction following the second of two closely successive administrations of Althesin, two had very high IgD concentrations. One of these patients and also the third reactant is clearly atopic. The families of two of these three reactors have been investigated also and show apparent correlation between inheritance of high concentrations of either IgE (atopy) or IgD. Obviously, considerably more work is required to substantiate our findings but, nevertheless, the significance of these observations must be viewed critically against three factors:

(1) The frequency of anaphylactoid reactions to Althesin (1 in 10 000).

(2) All three memory cases possess high concentrations of plasma immunoglobulins with cell-surface receptor properties.

(3) Only 5% of the population have IgD concentrations in excess of 85 iu ml^{-1}.

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INITIAL CLINICAL EVALUATION OF A HOLISTIC MODEL OF HUMAN RESPIRATION ("MACPUF") IN PATIENTS VENTILATED AFTER OPERATION

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Many models of human respiration have emphasized various aspects of the regulation of ventilation, gas transport and distribution. Although these models have been useful in describing traditional physiological mechanisms, their application to the management of clinical problems has proved more difficult. The model we have used ("MacPuf") (Dickinson, 1977) has been developed and improved successively over 8 years. It embodies a wide range of clinical knowledge and has been used successfully to describe retrospectively clinical problems in individual patients.

We have studied 12 patients who were being ventilated artificially following uncomplicated cardiac bypass surgery. We measured or derived all the information required by the model to simulate a subject on a ventilator. Measurements were made at intervals during the first 12–24 h after surgery until artificial ventilation was discontinued.

Initial attempts to match the model with the required data were made using manual estimations of parameters, but because of interactions within the model this proved difficult and time-consuming. Therefore, we designed a programme for automatic estimation of parameters. General details of subjects were entered and used to calculate a base-line steady state which was stored on a disc file for each patient. For each set of measurements, variables which are represented as preset parameters of the model were entered, with details of the regime of ventilation at the time of measurement. Parameters of the model representing metabolic activity, pulmonary shunt and deadspace were optimized automatically to match measured values for oxygen consumption and arterial blood-gas values.

At this point all the variables computed by the model could, in principle, be compared with clinical measurements and the need for more refined matching assessed. It is a reflection of the validity of MacPuf that correlation of arterial blood-gases, pulmonary shunt, deadspace and metabolic rate can be achieved with the model in a steady state. Accurate simulation of venous values and acid–base state will require further modifications to the matching procedure. Once this has been achieved an accurate steady state representation should be possible for any individual patient. This could be used predictively as an aid to the management of selected patients.

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BLOOD CONCENTRATIONS OF NITROUS OXIDE IN THEATRE PERSONNEL

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Assessment of the exposure of theatre staff to atmospheric contamination by anaesthetic agents should be made ideally from measurements of blood concentrations (Cole, 1976). Therefore, we have developed a gas-chromatographic technique for the measurement of small plasma concentractions of nitrous oxide (Saloojee and Cole, 1978), and have used this system to determine the extent of exposure of theatre personnel.

Anaesthetists, surgeons and nurses were studied while working in operating theatres with known ventilation characteristics. Standardized anaesthetic techniques were used with and without scavenging of waste gases. Samples of venous blood and ambient air from the subject's breathing zone were taken at prescribed intervals using gas-tight syringes and sampling bags, and a grease-free pump.

The results (table I) demonstrate that scavenging of waste gases can reduce blood concentrations of nitrous oxide by 90–95%. Surgeons were found to have the same or greater concentrations of nitrous oxide than anaesthetists, while the values for the circulating nurse were much smaller. The correlation between atmospheric and blood concentrations was poor in all groups ($r = 0.62$) and theatre ventilation rates did not appear to influence the results significantly.

The reductions in blood concentrations achieved by scavenging were produced only by careful attention to the prevention of leaks, and this could not be maintained in clinical practice. The unexpectedly great concentrations found in the surgeons suggest that this group may be more exposed to the risks of theatre contamination than had been thought previously. The lack of correlation between blood and atmospheric concentrations of nitrous oxide must raise doubts on the interpretation of previous work which is based on the measurement of nitrous oxide concentrations in ambient air.

TABLE I. *Nitrous oxide concentrations (p.p.m. and range) in theatre personnel*

Group	Mean blood concn	Mean ambient atmospheric concn
Anaesthetists		
With scavenging	33 (5–103)	54 (6–203)
No scavenging	266 (49–1127)	531 (52–2385)
Surgeons		
With scavenging	36 (20–198)	67 (20–207)
No scavenging	258 (58–764)	558 (96–1931)
Nurses		
No scavenging	65 (15–185)	93 (23–203)

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BLOOD CONCENTRATIONS OF DIAZEPAM FOLLOWING PARENTERAL ADMINISTRATION OF RO 03-7355, A NEW BENZODIAZEPINE PRODRUG

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Diazepam is insoluble in water and for parenteral use it is dissolved in organic solvents. When administered i.v. this solution may cause pain on injection and thrombophlebitis (Hegarty and Dundee, 1977).

RO 03-7355 is a water-soluble benzodiazepine without intrinsic pharmacological activity, but on incubation with blood it is hydrolysed rapidly to release diazepam. In the present study RO 03-7355 was administered parenterally to healthy unpremedicated volunteers and plasma diazepam concentrations were measured by gas–liquid chromatography (Zingales, 1973).

Initially, five subjects received, i.v., equipotent doses of diazepam and RO 03-7355 on separate occasions. Subsequently further subjects received RO 03-7355 i.m.

Following diazepam 5 mg i.v., peak plasma concentrations occurred in samples taken 2 min after injection and these were on average 1.6 times greater than those found after an equivalent dose of RO 03-7355. Following RO 03-7355 9 mg i.v., peak plasma concentrations of diazepam occurred at 10–15 min after injection and were 1.4 times greater than those observed after an equivalent i.m. dose, when the peaks occurred 30–60 min after injection (fig. 1).

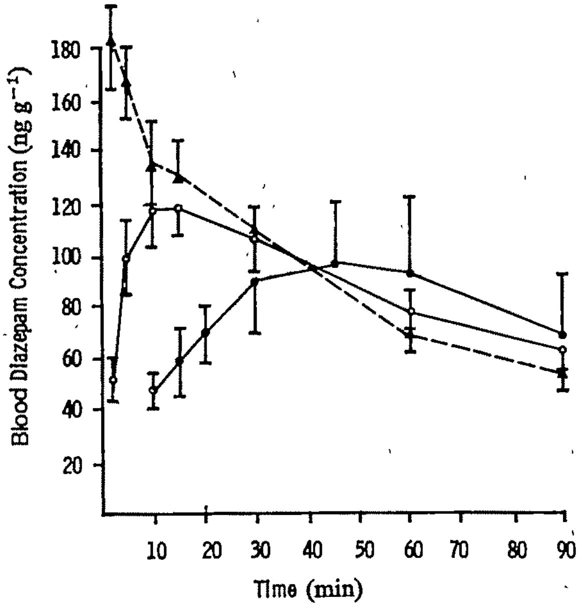

FIG. 1. Blood diazepam curves (±SEM) following diazepam 5 mg i.v. (▲), RO 03-7355 9 mg i.v. (○), and RO 03-7355 i.m. (●).

RO 03-7355 i.v. did not produce the same changes in conscious state as did an equivalent dose of diazepam. Following i.m. RO 03-7355, observable effects occurred after 15 min, although there were wide individual variations in the level of consciousness. Local tolerance was good following i.m. and i.v. RO 03-7355.

RO 03-7355 i.v. does not appear to be a suitable replacement for diazepam in minor surgical procedures, although i.m. administration may be useful in providing sedation before operation and in the management of epilepsy and psychiatric disorders. It is not known if entero-hepatic recirculation described by Baird and Hailey (1972) will prolong significantly the duration of plasma diazepam activity following RO 03-7355 i.m.

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MEASUREMENT OF AIRWAYS RESISTANCE DURING ANAESTHESIA

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Measurements of changes in airways resistance during anaesthesia cannot be interpreted unless reference is made to the lung volume at which measurement is made as there is a hyperbolic relationship between airways resistance and lung volume. Thus, at small lung volume, small changes in volume will produce very large changes in resistance. The whole-body plethysmograph permits the simultaneous measurement of airway resistance and lung volume, but is unsuitable for patients undergoing general anaesthesia and surgery.

To provide a system for the measurement and plotting of resistance–volume curves in anaesthetized, paralysed patients we have modified the forced oscillation method described by Hyatt and others (1970). A specially designed anaesthetic circuit is used which permits intermittent slow inflation and deflation of the lungs over the vital capacity range. During this manœuvre a sinusoidal airflow is imposed on the airway by a pump delivering a stroke volume of 70 ml at 3 Hz. Airflow resistance is calculated automatically and continuously from measurements of airway pressure, oesophageal pressure and airflow. Resistance is plotted as a function of lung volume on an X–Y recorder.

We have studied 20 healthy anaesthetized patients. Our results confirmed the hyperbolic relationship between resistance and lung volume, but also demonstrated considerable individual variability in the curvature and position of the hyperbolic curves. We have expressed the varying shape of the curves in each patient as the resistance at residual volume (RV) +100 ml. We have defined RV as that lung volume at which resistance extrapolates to infinity. An almost 10-fold range of resistance at RV +100 ml was observed (range 0.49–4.20 kPa litre^{-1} s, mean 1.19 kPa litre^{-1} s). Large variability was also observed in the expiratory reserve volume (range <10 ml–886 ml, mean 342 ml) so that even greater variability in resistance at functional residual capacity was observed (range 0.11–4.07 kPa litre^{-1} s, mean 0.63 kPa litre^{-1} s).

With this technique the separate effects of changes in bronchomotor tone and lung volume on airway resistance can be determined, and the effects of individual anaesthetic agents studied.

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EFFECT OF NITROUS OXIDE ON B12-REQUIRING ENZYMES

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Lassen and others (1956) and Amess and others (1978) have shown that megaloblastic depression of bone marrow follows the long-term administration of 50% nitrous oxide in patients. These changes were accompanied by an abnormal deoxyuridine suppression test. Banks, Henderson and Pratt (1968) found that nitrous oxide inactivated B12 to the inactive oxidized analogue *in vitro*. Amess and colleagues postulated two possible mechanisms to explain the effects of nitrous oxide. The first, based on studies in bacteria, was that nitrous oxide oxidizes the cobalt of vitamin B12 so that it is unable to activate the enzyme methionine synthetase required to convert homocysteine to methionine. The second suggestion was that nitrous oxide interferes with the uptake of B12 by the cell membrane.

To investigate the former possibility we have assessed the effects of nitrous oxide on the only two B12-requiring enzymes found in mammals: methionine synthetase and methylmalonyl-CoA mutase.

Groups of rats were exposed in environmental chambers to a mixture of either 50% nitrous oxide in oxygen or room air, for varying periods of time. The effects of exposure to nitrous oxide on methionine synthetase were assessed by assay of the enzyme in liver. The effects of nitrous oxide on methylmalonyl CoA mutase were assessed by the urinary excretion of methylmalonic acid using continuous ether extraction followed by gas chromatography. The results showed that methionine synthetase activity declined by 81% within 30 min of exposure to nitrous oxide and was virtually absent in the 6-h sample. However, we were surprised to find that the excretion of methylmalonic acid remained unaffected by 24 h of exposure to nitrous oxide.

The striking effect of nitrous oxide on methionine synthetase confirms that nitrous oxide suppression of deoxyuridine uptake is mediated by an effect on the B12 coenzyme, methylcobalamin, of which the synthetase is the apoenzyme. The lack of effect of nitrous oxide on methylmalonyl-CoA mutase may be the result of the possibility that, *in vivo*, the B12 coenzyme for this reaction is in the deoxyadenosyl form, and this may be protected from the action of nitrous oxide.

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PREDICTING MALIGNANT HYPERPYREXIA

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Malignant hyperpyrexia (MH) is a rare disease occurring in about 1 in 190 000 of anaesthetics in the U.K. between 1967 and 1976 (Ellis, unpublished observations). It has been reported that patients who develop MH have certain characteristics (indicants) which may aid in the identification of patients at risk (Britt and Kalow, 1970). Unfortunately, the fact that these indicants occur frequently in the normal population is not taken into account and therefore the value of a particular indicant is not established. For example, 15% of patients developing MH have a squint, but this does not help the anaesthetist predict the probability of a patient with a squint developing MH. The application of Bayes' theorem to the data would provide useful clinical information.

One form of Bayes' theorem states

$$\Omega'' = \Omega' \times L$$

(Phillips, 1973), where

Ω'' is the odds of MH developing given the presence of an indicant

Ω' is the odds of MH developing given no information about the presence or absence of the indicant

L is the likelihood ratio of the indicant

$$L = \frac{\text{true positive proportion}}{\text{false positive proportion}}$$

For the indicant "squint" the true positive proportion is 15% (Ellis, unpublished observations) and the false positive proportion is 1.5%, since this is the proportion of normal people who have a squint:

$$\Omega'' = \frac{1}{190\,000} \times \frac{15}{1.5} = \frac{1}{19\,000}$$

Thus, the odds of developing MH increases from 1 in 190 000 where there is no knowledge about the patient to 1 in 19 000 if the patient has a squint. Using this technique the effects of other indicants such as "female aged 5–14 yr" ($L = 5.6$) can be taken into account, producing a further decrease of the odds to 1 in 3400.

Since not all anaesthetics are likely to induce MH, a correction can be applied so that only anaesthetic procedures using inducing drugs are considered.

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INHIBITION OF NEURONAL UPTAKE OF NORADRENALINE BY PANCURONIUM IN THE ISOLATED PERFUSED RAT HEART

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Pancuronium and its closely related analogue, Organon 6368, were studied at a high concentration (500 μmol litre^{-1}) for inhibition of the uptake of tritiated noradrenaline into neuronal sites (Uptake$_1$) and extraneuronal sites (Uptake$_2$) in the isolated perfused rat heart (Iversen and Salt, 1970). At this concentration both drugs caused almost total inhibition of Uptake$_1$ (fig. 1), whereas Uptake$_2$ was much less affected. Uptake$_1$ was investigated further at lower concentrations and both drugs were found to produce a dose-dependent inhibition (fig. 1). The IC$_{50}$ value (concentration causing 50% inhibition) for pancuronium was found to be 16.1 μmol litre^{-1} (11.8 μg ml^{-1}), which is of the same order of magnitude as the concentration at which chronotropic effects occur in the rat. It seems likely, therefore, that inhibition of neuronal uptake of noradrenaline plays a significant role in the aetiology of the chronotropic actions of pancuronium in this species. Furthermore, Organon 6368, which is devoid of chronotropic activity, was found to be less than half as potent in inhibiting Uptake$_1$ (IC$_{50}$ value 38.8 μmol litre^{-1}) compared with pancuronium.

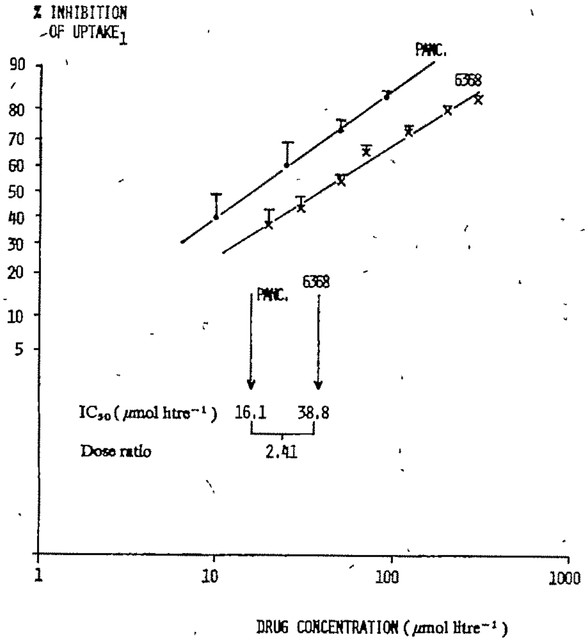

FIG. 1. Effect of pancuronium (panc.) and Organon 6368 on Uptake$_1$ of noradrenaline.

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BLOOD CONCENTRATIONS OF TRICHLOROETHANOL AFTER TRICHLOROETHYLENE ANAESTHESIA

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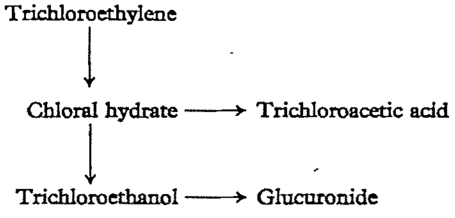
It has been known since 1939 that trichloroethylene is metabolized (Barrett and Johnston, 1939) and it is now thought that the path of metabolism is:



The extent to which trichloroethylene is metabolized is not known, although it is suspected that it is considerable. One of the metabolites, trichloroethanol, has a sedative action and the prolonged drowsiness often seen after lengthy trichloroethylene anaesthesia has been attributed to accumulation of trichloroethanol in the body.

Using gas chromatography, we have measured blood concentrations of trichloroethanol in a series of patients receiving trichloroethylene anaesthesia during periods of 1–6 h. Our results show that significant concentrations of trichloroethanol may be found in the blood during and after anaesthesia.

It is of interest that the peak of the mean concentrations of trichloroethanol was reached approximately 30 h after the end of administration of the anaesthetic. In general, there was a relationship between the concentration of trichloroethanol and the duration of anaesthesia, but considerable variation was found.

Trichloroethanol in one form or another has been used widely as a sedative and it appears to be safe and well tolerated. It has a plasma half-life of 8 h and is reported to have no analgesic properties (Goodman and Gilman, 1975).

After certain types of surgery, such as those in which artificial ventilation may be required for some time after operation, it may be considered desirable for patients to be sedated for 24 h or more after surgery, and in these instances trichloroethylene may have some advantages as an anaesthetic agent.

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ORGANIZATION OF A STUDY OF LIVER FUNCTION FOLLOWING REPEAT ANAESTHETICS

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The study of drug-induced liver dysfunction in the absence of jaundice is difficult as it involves biochemical monitoring in addition to clinical assessment. A prospective study of the effects on the liver of repeated inhalation anaesthetics has been in progress in Belfast since early 1976.

The greatest problem in this work is access to a distinct, easily identified patient population with a reasonable chance of requiring repeat anaesthetics within a period of less than 6 months. The patients must be relatively free from sepsis and not receiving therapy which would affect liver function adversely. Operations on the abdomen and thorax and blood transfusion are exclusion factors; one must be able to vary the form of anaesthetic safely at choice. These criteria are best fulfilled in patients presenting for endoscopic examination of the bladder and urethra, for urethral dilatation or for cervical implantation of radium. Such patients include a large proportion of outpatients, which makes time-consuming domiciliary follow-up necessary and requires a greater degree of patient co-operation. Since patient-to-patient variation in response to drugs is not known, one would require at least 50 patients in any group, so that worthwhile conclusions could be drawn; this will mean admitting at least twice that number to each study.

Blood samples were taken immediately before induction of anaesthesia and on the 3rd–4th and 13th–15th days after operation, when a clinical assessment of the patient was made. A "block" analysis of 20 electrolyte, protein and enzyme tests was carried out using Technicon SMAC (Sequential Multiple Analyser with Computer). Serum cholinesterase and gamma glutamyl transferase concentrations were estimated and a full haematological investigation was made. Six enzyme concentrations (lactate dehydrogenase, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, serum cholinesterase and gamma glutamyl transferase) and the eosinophil count were chosen as indices of liver function.

The organization of this study required very close co-operation with surgical and other colleagues. Operation lists had to be scrutinized for suitable patients and necessary arrangements made. Each patient was given an explanatory letter and a contact telephone number, together with details of expected home visits. Meticulous recording of data on computer-compatible charts facilitated analysis; appropriate statistical tests were applied for non-parametric data.

This study required a continuous staff of three full-time anaesthetists and a biochemist, as well as back-up facilities from the University Anaesthetic Department, in addition to laboratory, computer and secretarial personnel. It was under the supervision of two consultant anaesthetists and one consultant biochemist. It is estimated that over 3 years the study will have cost in excess of £125 000.

Br. J. Anaesth. (1979), **51**, 69

CORRESPONDENCE

ALTHESIN IN THE WOLFF–PARKINSON–WHITE SYNDROME

Sir,—Following two reports on electrocardiographic changes at induction in patients with the Wolff–Parkinson–White (W–P–W) syndrome (Hannington-Kiff, 1968; Campkin and Moore, 1969), Kadis and Gianelly (1973) question the use of thiopentone which appears to produce further aberrant conduction. Diazepam was suggested as the best induction agent, but its effect can be unpredictable in the younger adult patients, some failing altogether to become unconscious (Brown and Dundee, 1968). Since Althesin possesses useful anti-arrhythmia properties (Cundy, 1973), it may be a worthwhile alternative.

A 45-year-old female patient with asymptomatic W–P–W syndrome was undergoing laparoscopic ligation of the Fallopian tubes. Physical examination was normal apart from obesity and numerous varicose veins in both legs. A routine e.c.g. before operation showed the characteristic features of W–P–W syndrome although there was no history of attacks of tachycardia.

The patient was not premedicated, but atropine 0.2 mg was given slowly at induction. Anaesthesia was induced with Althesin 5 ml given over 2 min, and diazepam 5 mg. The trachea was intubated with the aid of suxamethonium 100 mg after pre-treatment with tubocurarine 3 mg, and before surgery was allowed to commence pentazocine 30 mg was administered. The e.c.g. was recorded at frequent intervals during the induction procedure (standard leads 1 and 2). No electrocardiographic modifications were observed at any time. After induction, anaesthesia was maintained with Althesin 1 ml every 5 min and tubocurarine (total 40 mg for a 1-h procedure). The lungs were ventilated artificially with 70% nitrous oxide in oxygen. Both anaesthesia and surgery proceeded uneventfully and recovery was normal. The heart rate was monitored continuously with a chest lead, but no changes in the e.c.g. occurred.

It would appear from this case that Althesin is a possible alternative to thiopentone for induction (and also for maintenance) of anaesthesia in these patients. The e.c.g. changes reported with thiopentone were suggestive of acute myocardial infarction, but were shown to be the result of further aberrant conduction as enzyme concentrations (s.g.o.t., s.g.p.t., LDH) remained normal. Aberrant conduction, although much less serious, may have profound circulatory effects (McIntosh and Morris, 1966; Boba, 1978).

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COMPARISON OF TRACHEAL CUFFS

Sir,—The article entitled "A Method for Comparing Endotracheal Tubes" (Homi et al., 1978) provides additional evidence to support the view that it is unnecessary to have a tracheal wall pressure greater than the peak airway pressure. However, in deducing the tracheal wall pressure for a low residual volume cuff from the compliance curves, the authors make the assumption that the cuff inflates to the same shape in air as it does in the confines of the trachea. This is clearly not so and the tracheal wall pressure will vary along the length of the cuff. Therefore, the resulting "calculated" pressure can only be an approximation. One major problem in the use of compliance curves is that the physical properties of a cuff will vary between individual tubes as a result of manufacturing tolerances and in a given tube they can vary with both temperature and time. For the high residual volume cuff, it has been shown that the intra-cuff pressure is equal to the tracheal wall pressure (Carroll, 1973; Crawley and Cross, 1975) and so compliance curves are unnecessary.

It is not always acceptable to use minimal leak ventilation as this may not provide protection against aspiration. In these situations additional air will need to be added to the cuff. For a low residual cuff the effects of this are not immediately apparent, whereas for the high residual cuff the effect can be seen readily by using a simple pressure gauge to measure the intra-cuff pressure and hence the tracheal wall pressure. Indeed, with the high residual volume cuff, additional air added to the cuff will, in the first instance, increase the resting cuff pressure without necessarily increasing the peak intra-cuff pressure. This is not so for a low residual volume cuff, as has been demonstrated again by Homi and his colleagues in their figure 5. From this it can be seen that the addition of 1 ml of air to the cuff almost doubles the calculated tracheal wall pressure.

Homi and his colleagues refer to a high transmitted pressure necessary for a seal in high residual volume cuffs "particularly along any folds or ridges in the cuff". They quote the reference as an earlier paper by myself (Cross, 1973). In fact, the higher pressures referred to were not "particularly along any folds" but were generally increased intra-cuff pressures necessary to seal any folds. This was only the case in the *in vitro* studies. Later work (Crawley and Cross, 1975) showed that these greater pressures were not necessary in the clinical situation. This was probably because of thinner cuffs that had become available since the earlier work and also the action of mucus in sealing any minor leaks.

It is debatable if significant differences in resulting tracheal injury occur from various cuff designs when they are adjusted to exert a similar pressure on the mucosa. The difficulty is in knowing what pressure is being exerted in the case of low residual volume cuffs. It should be remembered also that in this instance the tracheal wall pressure is virtually static (at the peak value). In the case of the high residual volume cuff, this is not the case as the intracuff and tracheal wall pressure respond in a dynamic fashion to the airway pressure. It is quite possible to maintain a seal against a peak airway pressure of 40 cm H_2O or greater with a resting cuff pressure of only 10 cm H_2O. Therefore the comparison of tracheal pressures between the two types of cuff is difficult. The value of referring only to peak pressures is debatable and a time-weighted average pressure would perhaps be more appropriate.

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Sir,—We are most grateful for the interest shown in our work by Mr Cross of Portex Ltd, and for the opportunity to reply. We agree that our calculation of wall pressure is an approximation, albeit a decided improvement on previous methods, and that calculations of wall pressure from compliance curves would be inappropriate in anaesthetic practice. The sole purpose of our calculation was to demonstrate that, in the presence of a minimal airway leak, peak tracheal wall pressure is equal to peak airway pressure. In long-term airway management, airway pressure is always monitored, so that, in contrast to cuff pressure (which is seldom measured in practice), peak airway pressure is readily available as a guide for correct cuff inflation.

We find that minimal leak ventilation is an adequate protection against aspiration and has the added advantage of preventing gastric contents pooling above the cuff and thus damaging the trachea. We certainly do not recommend that a low residue cuff should be inflated until all leaks are prevented: this will result in a dangerously high tracheal wall pressure.

When the recommended size of tracheal tube is positioned within the trachea, high residual cuffs remain compressed and extremely folded, so that after inflation their actual shape is very different from the usual illustrations showing rounded, balloon-shaped cuffs supporting and cushioning unrealistically small endotracheal tubes.

The main purpose of our study was to compare cuffs of different design exerting the same pressure on the tracheal mucosa. Although we agree that resting tracheal pressure is greater for a low residue cuff than for a high residue cuff at the same peak airway pressure, we found that for a given peak pressure, no difference in tracheal damage could be detected. Therefore we conclude that, when correctly used, high residue cuffs show no clear advantage over low residue cuffs.

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TEST-DOSE IN EXTRADURAL ANALGESIA

Sir,—Dr Galloon (1978) in answer to Dr Scott (1978), advocates the use of a test-dose with each top-up of an extradural block and reported that a subarachnoid block had occurred although the first injection seemed to indicate that the catheter was in the extradural space. This phenomenon has been reported previously by Philip and Brown (1976), who noted that the patient required endotracheal intubation after the second injection through a catheter (with no side-holes) of 7 ml of 0.5% bupivacaine. Bonica (1967) reported four cases in 16 000 caudal extradural blocks; in two mothers a total spinal block developed after the third injection and in the other two mothers after the fourth injection.

Scott (1978) responded that, if a test-dose were used at each top-up, then "the whole practice of midwives' topping-up would have to be abandoned as it is clearly unfair to expect nurses to decide if the test-dose has been injected into the subarachnoid space".

Fortunately, patients requiring urgent resuscitation seem to be uncommon. Indeed Crawford (1977) wrote that he was unconvinced that there is any practical danger: "We have provided an epidural for close on 13 000 labouring patients . . . and on three or four occasions there has undoubtedly been an inadvertent injection of bupivacaine into the CSF (with twice extension of the block to a similar level" (that is, T2), "we have never required to assist a patient's ventilation. . . ."

In Cardiff all top-ups are performed by an anaesthetist. In more than 4000 deliveries, two instances of accidental subarachnoid insertion of the catheter were recognized immediately, but a third was not until after the first injection through the catheter.

It is clear that an accidental spinal block may be recognized immediately the catheter is inserted, at the time of injection of the local anaesthetic, or not until a later injection. This latter situation may result either from late perforation of the dura by the catheter, or because the catheter is only partially in the extradural space. The design of some catheters, with openings at a distance from the tip, may easily lead to this complication. Factors such as the rate of injection may be important also, if only one opening is in the subarachnoid space (Hartley, 1975).

This hazard is potentially serious. Unfortunately only the report of a death associated with a "top-up" would persuade everyone that there is a real risk. However, even without that information, prudence should dictate that each "top-up" should be carried out by someone capable of resuscitating a paralysed, or partially paralysed, patient. Usually this will be an anaesthetist or, sometimes, an obstetrician. Scott's (1978) opinion of the midwives' role must be taken seriously, since the midwife cannot be allowed to determine the dose. Therefore, unless a dose can be defined which could never result in respiratory embarrassment, there must be a real, if small, danger when this duty is delegated to a midwife. It would be difficult to justify a mother's death merely on the grounds of convenience.

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BUPRENORPHINE FOR POSTOPERATIVE ANALGESIA

Sir,—We would like to comment on the two recent papers by Kamel and Geddes (1978) and Kay (1978) describing the use of buprenorphine for pain relief after operation. Kamel noted a lower frequency of nausea, drowsiness and dizzyness following buprenorphine 50 μg kg^{-1} compared with pethidine 1 mg kg^{-1}. Kay reported an increased frequency of drowsiness in the group treated with buprenorphine in comparison with morphine, although he found the frequency of nausea and vomiting was the same for both drugs.

Recently we have studied a group of 120 fit adult patients receiving either buprenorphine 0.3 mg or morphine 10 mg i.m. as a premedicant before elective surgery. Neither atropine nor hyoscine was included with the premedication. The two groups were matched for age, weight and sex, and the types of operations. The patients were assessed in the anaesthetic room for any adverse effects of the premedication by an independent nurse observer who was unaware which drug was given. The mean intervals between drug administration and preoperative assessment were 59 min (SD ± 22) for buprenorphine and 66 min (SD ± 17) for morphine respectively. The frequencies of nausea and vomiting, and giddiness were greater in the buprenorphine group than the morphine group (table I).

TABLE I. *Frequency of side-effects in patients given morphine or buprenorphine for premedication. The difference between the drugs was significant* ($P < 0.05$) *for each effect*

	n	Awake	Nausea + vomiting	Giddiness
Morphine 10 mg i.m.	65	45 (69%)	2 (3%)	7 (11%)
Buprenorphine 0.3 mg i.m.	55	26 (47%)	8 (14.5%)	12 (22%)

Four patients in the buprenorphine group experienced a sensation of floating or light-headedness before surgery, while a further three patients receiving buprenorphine complained of episodes of double vision.

The patients who received buprenorphine as premedication required less analgesia after operation in our series. Of those patients who needed pain relief after surgery, 6% of the buprenorphine group as compared with 32% of the morphine group received analgesics during the first 9 h ($P < 0.05$).

We would agree, therefore, that buprenorphine as an analgesic is superior to morphine, but when given alone as a premedicant has a higher and, we believe, unacceptable frequency of adverse side-effects.

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BEFORE CANNULATION OF THE RADIAL ARTERY

Sir,—Because prospective studies have revealed a 40% frequency of thrombosis of the radial artery following cannulation (Bedford and Wollmann, 1973; Palm, 1977), during the last year we have routinely measured distal arterial pressure in the thumb before and after compression of the radial artery, to ensure the presence of adequate collateral flow through the ulnar artery.

Recent results in patients undergoing vascular procedures differ from those obtained in our study of arterial dominance in the hand in 100 younger, healthy subjects (Husum and Palm, 1978).

In 139 patients (46 females) undergoing elective vascular or open heart surgery, 272 hands were examined before operation. The age range was 14–76 yr (median 55.1 yr). Arterial pressure was measured simultaneously in the thumb and in the contralateral arm using strain-gauge plethysmography before and after compression of the radial artery (Gundersen, 1972; Husum and Palm, 1978).

In 30 patients, simultaneous determination of the systemic arterial pressure in the two arms revealed differences ranging from 11 to 60 mm Hg (median: 16.5 mm Hg).

In 66 hands (24%), compression of the radial artery did not reduce the arterial pressure in the thumb, thus perfusion pressure through collaterals was adequate to compensate fully for the decrease in flow produced by occluding the radial artery.

In 206 hands (76%) compression of the radial artery reduced the arterial pressure in the thumb by more than 10 mm Hg, and in 20 hands in 15 patients the pressure decreased to less than 40 mm Hg (a value associated with clinical symptoms of inadequate blood supply (Lassen et al., 1975)). In 10 patients the inadequate collateral supply was seen only unilaterally. In four of the five patients in whom the examination indicated bilateral inadequate collateral ulnar arterial supply, none of the radial arteries was cannulated. In one patient the artery was cannulated, and fortunately there were no signs of occlusion of the artery after operation.

We conclude that, because 15 of 139 patients (10.7%, 95% confidence limits 6.1–17.8%) would be without adequate blood supply to the thumb following occlusion of the radial artery, cannulation of the radial artery for pressure monitoring and blood sampling should be performed only after ensuring the presence of an adequate collateral ulnar arterial supply. We find that measuring the distal arterial pressure in the thumb before and after compression of the radial artery is a convenient method.

B. Husum
T. Palm
Copenhagen

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Palm, T. (1977). Evaluation of peripheral arterial pressure on the thumb following radial artery cannulation. *Br. J. Anaesth.*, **49**, 819.

CARDIORESPIRATORY ARRESTS—A DIURNAL VARIATION?

Sir,—Most major hospitals in the U.K. operate a "crash call" system whereby medical staff can be summoned urgently to attend a patient with cardiorespiratory arrest. We have undertaken a study to determine if such arrests occur either at random or at particular times of the day.

A retrospective study was made of the case records of 248 patients undergoing cardiopulmonary resuscitation (CPR) at a busy district general hospital in a period of 27 months from August 1975 to October 1977. All the case records were reviewed, but some were excluded from the study if: (a) the arrest occurred at home or in an ambulance, when the timing and diagnosis were potentially uncertain (18 patients); (b) the time of the arrest was not stated in the hospital notes (2 patients); (c) the arrest appeared to be related directly to surgery or anaesthesia (10 patients).

The CPR calls for the remaining 218 patients were not distributed evenly over the 24-h period (fig. 1), and the common clinical impression that arrests are more common at night appears to be unfounded. In fact there were a greater number of CPR calls in the period between noon and midnight (60.5%), compared with the period between midnight and noon (39.5%) ($\chi^2 = 9.7064$, $0.001 < P < 0.01$). Two "peak periods" of calls occurred between 13.00 h and 15.00 h, and again between 18.00 h and 21.00 h—these peak periods accounted for 34% of all calls.

We suggest the following possible reasons for the observed variation in the incidence of CPR calls:

(i) Failure to diagnose cardiac arrest rapidly at night (although in this study a high proportion of calls originated in the intensive care unit, where this type of failure should be less likely).

(ii) Inadequate reporting of night calls—although record-keeping of the patients studied was excellent in all other respects.

(iii) Higher levels of stress and autonomic activity in awake patients, possible accentuated at the observed peaks by meals, hospital visitors and other factors.

(iv) A true diurnal variation in the incidence of cardiorespiratory arrest.

We would be interested to hear if this phenomenon has been observed elsewhere.

R. J. Eltringham
M. B. Dobson
Gloucester

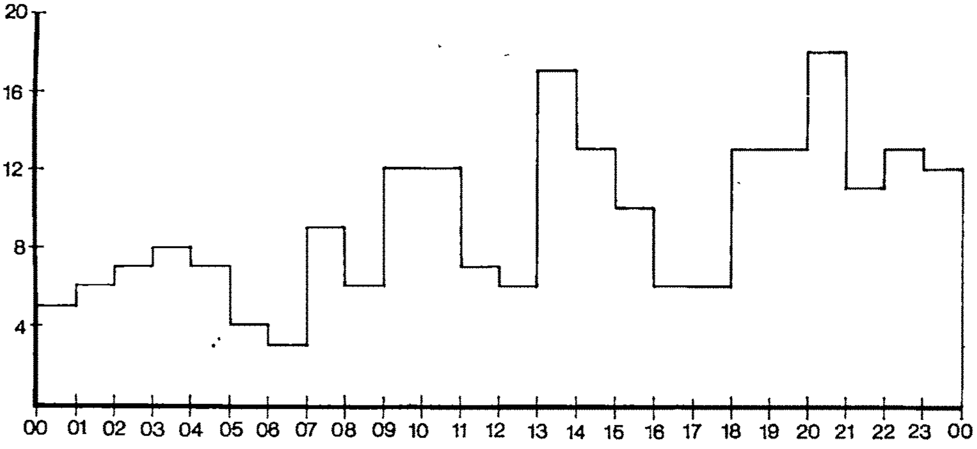

FIG. 1. Histogram of cardiac arrest with respect to time of day.

INSERTION OF NASOGASTRIC TUBES

Sir,—The article by Dr Sweatman and colleagues (1978) reminded me of that facetious medical adage: "If all else fails, examine the patient." On separate occasions in their article they state that "if necessary" and "if there is doubt" direct laryngoscopy must be used. Surely any attempt at oesophageal intubation requires direct laryngoscopy.

The cases of Saha (1974), Seebacher, Nozik and Mathieu (1975), case 1 (and, I suspect, case 2) of Sweatman and colleagues (1978) all had oesophageal devices passed blindly. In at least three of these patients, complications could have been avoided had the instrumentation been carried out under direct vision. If there is to be a message it is: "It is clearly desirable to pass the nasogastric tube (or any oesophageal device) under direct vision whatever technique is employed" (Saha, 1974).

C. VAN DER WEYDEN
Annandale, Australia

REFERENCES

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Sir,—Dr Sweatman and colleagues (1978) describe an elaborate method of insertion of a nasogastric tube.

The following method is simpler, but applies to paralysed patients only.

After negotiating the nasal cavity with a nasogastric tube, the whole larynx is elevated by gripping the thyroid cartilage between thumb and fingers and lifting. The nasogastric tube then slides down the oesophagus without hindrance.

The procedure is easier in males because of their more prominent thyroid cartilage.

Providing the gripping of the larynx is performed carefully, no harm should result.

WILLIAM F. S. SELLERS
Gloucester

REFERENCE

Sweatman, A. J., Tomasello, P. A., Loughhead, M. G., Orr, M., and Datta, T. (1978). Misplacement of nasogastric tubes and oesophageal monitoring devices. *Br. J. Anaesth.,* **50,** 389.

Sir,—Thank you for the opportunity to reply to Dr Sellers and Dr van der Weyden.

We agree with Dr Sellers that forward movement of the larynx will allow a nasogastric tube to enter the oesophagus more easily. We prefer to achieve this by anterior displacement of the mandible rather than gripping and elevation of the larynx, which may be painful and compress the carotid arteries and carotid sinus.

In reply to Dr van der Weyden, direct laryngoscopy is undoubtedly the best way to confirm the position of a nasogastric tube. However, in the situation we describe—multiple oesophageal intubations in anaesthesia for cardiac surgery—as many as five tubes or devices may be taped in position so that the mouth and pharynx are too crowded to allow a direct view. In other situations, such as intensive care units, patients may not be paralysed and the non-medical personnel to whom the task of inserting nasogastric tubes may be given are usually not trained to use the laryngoscope.

The aim of our method was to provide a means of avoiding and detecting misplacement without the use of any extra equipment other than hands, eyes and ears.

ALAN J. SWEATMAN
PHILIP A. TOMASELLO
MICHAEL G. LOUGHHEAD
MALCOLM ORR
TAPAN DATTA
Baltimore, U.S.A.

ANAESTHESIA AND INFANT WEIGHT

Sir,—I found the recent article by Abouleish and colleagues (1978) provocative but erroneous. The authors examined the interesting hypothesis that the effects of maternal analgesia on the neonatal central nervous system might be sufficient to alter the change in weight that occurs after birth. They base this concept on the well-known properties of various agents used in obstetrics to influence many newborn behaviour patterns, including nutritive and non-nutritive sucking. They tested their hypothesis by performing a 2-year retrospective analysis of vaginal deliveries, randomly selected for type of anaesthesia. They assessed the change in weight of the infant, which reflects newborn fluid balance, and not necessarily the infant's ability to feed, suck or be other than minimally intact neurologically. Thus their study was marred from the outset.

They excluded 50% or more of deliveries selected under each category. For example, we are not informed of the reasons for excluding 68 natural childbirth mothers from the study.

In the analysis, they chose standard error of the mean (SEM) rather than standard deviation as a measure of central tendency. However, when SEM is converted to standard deviation (by multiplying the former by the square root of n), the enormous variance in weight and weight change within and between groups is evident. This leads to the conclusion that early, short-term neonatal weight is a useless measure of subtle changes in central neurological function which may be induced by drugs administered to the mother.

Abouleish and his colleagues have merely demonstrated that infants who have access to fluid (the bottle) will gain weight after their acute fluid loss has occurred, while those with limited access to fluid (the prelactating breast) will not demonstrate an increase until fluid is available (lactation). Whether such differences are good or bad is, of course, unknown. In summary, their attempt to reassure us of the absence of neonatal effects from maternal drugs is inconclusive.

JOHN W. SCANLON
Washington

REFERENCE

Abouleish, E., Van der Donck, A., Meeuwis, H., and Taylor, E. (1978). Effect of anaesthesia for delivery on the weight of infants during the first 5 days of life. *Br. J. Anaesth.,* **50,** 569.

Sir,—Thank you for the opportunity of replying to Dr Scanlon's letter, which contains four major comments.

The basis of our study: We did not claim, in any part of our article, that neonatal weight changes should replace neurobehavioural tests in evaluating anaesthetic drugs. We wondered if these agents, which he stated in his letter "to influence many newborn behaviour patterns including nutritive and non-nutritive sucking", would ultimately affect the neonatal weight. This basis was clearly defined in the "Introduction" section of our article.

Selection of the cases: Out of 600 cases, only 241 babies met the criteria for selection. The others were excluded because their mothers had received narcotics, tranquillizers, paracervical block or developed hypotension or premature onset of labour. The aim was to have six groups in which the only variable was the anaesthetic. This, again, was clearly stated in the "Method" section of our article.

Statistical analysis of the data: The statistical procedures employed in the data analysis are those of "analyses of variance of repeated measurements" (Winer, 1962). Consistent with these procedures, as with any analysis of variance procedure, the *standard errors* of the respective means are given, not the standard deviation of the observations themselves. Since the sample sizes are also given, Dr Scanlon, if he chooses, can make the known conversion. The obfuscation that might arise would do so if the sample sizes were omitted and he had only the value of the standard error. It is the sample mean that has been chosen as an index for comparison purposes among the various groups, and this is a standard analytical procedure.

The difference in weight changes between bottle- and breast-fed neonates: In order to compare the effects of different anaesthetics, the method of feeding had to be taken into consideration. The difference we found between the bottle- and breast-fed neonates in the various anaesthetic groups was reported, as it should have been. Dr Scanlon's explanation that the difference we found is a matter of access to fluid is too simplistic an approach. The difference is, in fact, a result of multiple factors including the difference in composition between the artificial and natural milk during the early days of lactation. The enthusiastic mother, in the bottle-fed group, supplies her child with all the measured and predetermined quantity of milk, irrespective of need.

Neurobehaviour studies of infants were described originally by Prechtal and Beintema (1964), Beintema (1968) and Brazelton, Robey and Lother (1969). When Dr Scanlon modified these tests for evaluating local anaesthetics he stated: "The implications [of these tests], if any, for future growth and development remain to be elucidated (Scanlon et al., 1974)". Neonatal weight changes is one criterion for neonatal growth and development. Thus, our study, at least in our opinion, is a step in the right direction for determining the clinical value of these tests.

In conclusion, we feel that Dr Scanlon did not read our study carefully and he misinterpreted the results.

E. Aboulеish
F. Taylor
Pittsburgh

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DIAZEPAM IN CARDIAC SURGERY

Sir,—In the recent article by Jackson and colleagues (1978), a significant change in mean arterial pressure was found after the administration of diazepam 0.4 mg kg^{-1} during the induction of anaesthesia for patients undergoing coronary bypass surgery. The subsequent administration of ketamine 2 mg kg^{-1} produced no significant change in mean arterial pressure. In 10 patients undergoing coronary artery bypass surgery, anaesthesia was induced with diazepam 0.1 mg kg^{-1} and ketamine 1.0 mg kg^{-1} followed by pancuronium 0.1 mg kg^{-1} in 60-s intervals. The patients breathed 100% oxygen during the administration of drugs and were ventilated manually during the investigation. There was no decrease in mean arterial pressure (table I). We believe, therefore, that the decrease in arterial pressure may be avoided by giving less than 0.4 mg kg^{-1} diazepam for the induction of anaesthesia. Similar results have been obtained in patients undergoing cardiac valve replacement.

TABLE I. *Cardiovascular responses to diazepam 0.1 mg kg^{-1} in patients undergoing coronary artery bypass surgery*

	Time (min)				
	0	2.5	5	7.5	10
Arterial pressure (mm Hg)					
systolic	140	148	142	145	151
diastolic	77	91	86	79	90
mean	98	109	104	101	110
Heart rate (beat min^{-1})	92	102	105	103	103
Central venous pressure (mm Hg)	7	10	9	9	9

A. Barankay
Budapest, Hungary

REFERENCE

Jackson, A. P. F., Dhadphale, P. R., Callaghan, M. L., and Alseri, S. (1978). Haemodynamic studies during induction of anaesthesia for open-heart surgery using diazepam and ketamine. *Br. J. Anaesth.*, **50**, 375.

ACID ASPIRATION SYNDROME

Sir,—I have just re-read the paper by Hester and Heath (1977) and realize that they have misquoted our work (Hutchinson and Newson, 1975). They state that mortality from pulmonary acid aspiration syndrome in all hospitals in Auckland between 1967 and 1969 was 1 in 11 000 of non-obstetric patients. In fact, 1 in 11 000 was the frequency of severe pulmonary acid aspiration syndrome in all operative cases during that 3-yr period, including obstetric patients. The mortality (which regrettably was not quoted in our paper) was 10% of the morbidity, or 1 in 110 000, before the use of magnesium trisilicate mixture.

In the 3-yr period 1970–72, when magnesium trisilicate was coming into routine use, the frequency of severe pulmonary acid aspiration syndrome in all operative cases (including obstetrics) was 1 in 40 000. The mortality was 1 in 120 000, which one must admit was not very different from the period before antacid therapy. It is interesting to note that none of our 13 patients with severe acid aspiration syndrome during the 6 years had received antacid before anaesthesia.

Currently we are analysing the frequency of Mendelson's syndrome during the years 1973–78, and this should indicate if the routine administration of a magnesium trisilicate mixture before operation has been justified.

B. R. HUTCHINSON
Auckland, New Zealand

REFERENCES

Hester, J. B., and Heath, M. L. (1977). Pulmonary acid aspiration syndrome: should prophylaxis be routine? *Br. J. Anaesth.*, **49**, 595.

Hutchinson, B. R., and Newson, A. J. (1975). Pre-operative neutralisation of gastric acidity. *Anaesth. Intens. Care*, **3**, 198.

Sir,—We hope that Drs Hutchinson and Newson will forgive us for our carelessness in substituting mortality for frequency. We apologize unreservedly.

It is interesting to note the apparent failure of magnesium trisilicate therapy to reduce significantly the mortality rate from acid aspiration.

We await the results from New Zealand with interest to see if they do indeed confirm that magnesium tricilicate, as well as being cheap and safe, is actually effective. It is possible that the anaesthetic mortality survey (Scott, 1978) to be undertaken under the auspices of the Association of Anaesthetists of Great Britain and Ireland may produce comparable information in Great Britain.

M. L. HEATH
J. B. HESTER
London

REFERENCE

Scott, D. B. (1978). Editorial. *Anaesthesia*, **32**, 977.

DIFFICULT INTUBATION

Sir,—In response to the correspondence by Dr Dennison (1978) on intubation of a patient with Still's disease, I should like to describe a recent case of difficulty in endotracheal intubation at the University of Tübingen.

A young 24-year-old female patient suffering from generalized fibromatosis presented for extensive surgery of the upper and lower jaws combined with multiple dental extractions. All the muscles of the patient were of bone-like consistency and ankylosis of the tempero–mandibular joints did not allow separation of the teeth by as much as 1 mm. There was no movement of the cervical spine and the larynx was completely imobile.

Anaesthesia was induced with small quantities of etomidate which permitted good spontaneous ventilation. A soft latex armoured tube was well lubricated and passed through the nose and pharynx (which had been anaesthetized previously with local analgesic) until respiratory sounds were heard maximally through the tube. At this point, a lignocaine aerosol spray was passed through the tube and approximately 80 mg of lignocaine introduced, producing paralysis of the vocal cords within 2–3 min. This allowed subsequent easy blind nasal intubation in the anaesthetized patient breathing spontaneously. Insertion of the tube into the larynx was accomplished by rotation and advancement with the guide of breath sounds.

J. HAUSDOERFER
Tübingen, West Germany

REFERENCE

Dennison, P. H. (1978). Four experiences in intubation of one patient with Still's disease. *Br. J. Anaesth.*, **50**, 636.

ENDOTRACHEAL INTUBATION IN STILL'S DISEASE

Sir,—If the arthritic patient referred to by Dr Dennison (1978) had presented only for tracheal intubation, then he and his colleagues could be applauded for their perseverence. As the patient required hip surgery, they should have considered alternatives to endotracheal anaesthesia. Spinal or extradural anaesthesia provide good operating conditions for hip replacement and are usually possible even with advanced arthritis of the spine.

Local anaesthesia would have avoided the measures described, which carried the potential risk of endangering the larynx and subluxing the odontoid peg.

As Aesop might have said: "If at first you don't succeed, discretion is the better part of valour."

J. DAVID GREAVES
Queensland, Australia

REFERENCE

Dennison, P. H. (1978). Four experiences in intubation of one patient with Still's disease. *Br J. Anaesth.*, **50**, 636.

Sir,—Thank you for the opportunity to reply to the letter of Dr Greaves. I do not agree that a technique of extradural or spinal analgesia could ever be as satisfactory or safe as general anaesthesia for hip replacement. Patients prefer general anaesthesia. Local anaesthetic techniques are not always successful, and they may be impossible to perform. Analgesia may not last the duration of surgery, "topping up" may be dangerous after blood loss, the inevitable hypotension is dangerous in the elderly, and anticoagulants are often present. In addition, intubation should always be available when the technique is used.

While aware of the possibility of subluxation of the odontoid peg in patients with rheumatoid arthritis, I have not seen this condition in many years, or heard of a case other than in patients suffering from trauma.

At Miss C. W.'s first visit, difficulty in endotracheal intubation was not expected (my own error!). The decision to abandon the operation was, I am sure, correct. Apart from a sore throat, she was in excellent health and spirit after anaesthesia. On the second, third and fourth visits, endotracheal intubation was performed under local analgesia and basal sedation, with extreme care and gentleness; she remembered little of the second visit, and nothing of the third and fourth, to her chagrin, as she took an intense interest in the problem.

I agree entirely with Dr Greaves that retrograde cannulation of the larynx is potentially lethal; even a small haematoma between the cartilage and the mucosa of the trachea would be very dangerous in a patient in whom it is impossible to intubate the larynx quickly, and tracheotomy would be very difficult. I have been forced to use this procedure six times in my orthopaedic practice, and it was to avoid this specifically that the fibreoptic laryngyscope was obtained. It is not always successful, but it is a very useful piece of equipment.

While enjoying Aesop, I feel Dr Joad might have said: "It all depends what you mean by 'discretion'."

P. H. Dennison
Birmingham

GLUCOSE TOLERANCE DURING SURGERY AND EXTRADURAL ANAESTHESIA

Sir,—In their report Houghton and colleagues (1978) stated that a normal glucose tolerance and insulin release were observed under extradural analgesia, and that general anaesthesia produced decreases in both glucose tolerance and insulin release.

There are, however, some objections relevant to these conclusions: First, the two groups studied are not comparable, since the mean control K-value is significantly ($P < 0.05$) *smaller* in the extradural group, which, therefore, may represent another population. This is supported further by the fact that these patients also had the greatest fasting insulin values (table II in their article).

Second, although the glucose data in the general anaesthesia group show a decreased glucose tolerance ($P < 0.001$), the few insulin values neither permit nor indicate a statistically significant decrease in the release of insulin.

Therefore, further studies are needed before any conclusions on the effect of extradural anaesthesia on glucose tolerance and insulin release during or following surgery can be made.

Henrik Kehlet
Mogens R. Brandt
Holstebro, Denmark

REFERENCE

Houghton, A., Hickey, J. B., Ross, S. A., and Dupre, J. (1978). Glucose tolerance during anaesthesia and surgery. Comparison of general and extradural anaesthesia. *Br. J. Anaesth.*, **50**, 495.

Sir,—Thank you for the opportunity of replying to Drs Kehlet and Brandt.

Although I agree that the two groups are not matched perfectly as regards their control K values, this does not preclude a comparison of the K value differences (control − operative (general) *v.* control − operative (extradural)). Within-patient comparison is the key to our method. Merely to amass operative plasma glucose and insulin data would appear to be of more limited value.

Certainly the few insulin values do not allow formal statistical analysis, but again within-patient comparison renders them more meaningful, if not "significant".

A. Houghton
Dundee

SPREAD OF SOLUTIONS IN THE EXTRADURAL SPACE

Sir,—We were most interested in the statistical study by Grundy and others (1978), since their findings concerning the spread of solutions in the extradural space, based on resultant levels of analgesia, correspond closely with our results based on radiological studies (Burn, Guyer and Langdon, 1973). In particular, the relation of the spread of analgesia to the volume injected shows wide variations and cannot be predicted accurately; there is only a poor correlation between the height of the patient and the degree of spread. In addition the rate of injection is not significant, a conclusion reached also by Nishimura, Ketahara and Kusakabe (1959) using radioisotope tracers. We agree that the influence of age on the degree of spread is minimal; indeed in our series there was no correlation. In agreement with Nishimura also, we could not show any influence of gravity on the spread of the solution, and it is interesting that Grundy and collegues found asymmetrical levels of analgesia in less than 14% of patients and even these could be accounted for by causes other than gravity, for example, the cannula tip deviated from the midline, or the presence of septa.

An investigation of the levels of analgesia and the spread of radio-opaque solution in the same patients would be of considerable interest.

James M. B. Burn
L. Langdon
Southampton

REFERENCES

Burn, J. M. B., Guyer, P. B., and Langdon, L. (1973). Spread of solutions injected into the epidural space. *Br. J. Anaesth.*, **45**, 338.

Grundy, E. M., Rannamurthy, S., Patel, K. P., and Winnie, A. P. (1978). Extradural analgesia revisited. *Br. J. Anaesth.*, **50**, 805.

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Br. J. Anaesth. (1979), **51**, 77

BOOK REVIEWS

Editors' note.—The review of *Anesthesia for Neurological Surgery: International Anesthesiology Clinics, Vol. 15, No. 3*, which appeared in the September issue of this Journal (Vol. 50, p. 976) was furnished by Professor D. G. McDowall. We apologize for the fact that Professor McDowall's name was omitted from the published report.

Clinical Parenteral Nutrition; The Proceedings of a Parenteral Nutrition Workshop. April 1977. Edited by D. H. Baxter and G. M. Jackson.

Professor R. Shields states in the introduction: "We are going to be concerned with operational tactics" and "How could this fact and that theory improve the care of patients who have nutritional problems". The editors emphasize these words with bold type. However, the aim is never fulfilled. The first 51 pages contain, at the most generous estimate, only two pages dealing directly with parenteral nutrition, and one questions whether the title "Workshop" is justified.

The clinical aspects of prolonged parenteral nutrition by Professor A. H. G. Love are of interest, but his account lacks detail. It is only in the discussion that a reference is given to trace elements and then only that they were given weekly. Chapters such as those of Balstone and Alberti and of Smith and Wells justify attention. The diagrams and figures are particularly helpful. The contribution by Dr G. C. Wise on "Patenteral Nutrition in Intensive Therapy Patients" will appeal to those readers whose duties lie in this field because of its controversial content.

Although Dr Paymaster (on the role of parenteral nutrition in gastrointestinal surgery) derived the standard error for various values in 14 patients receiving Aminoplex 5, little benefit accrues to the reader, as the control group contained only one patient.

The editors must be criticized for several reasons. The most significant is that not all of the figures and tables can be understood without reference to the text. There is also a lack of uniformity of choice of units—in some instances two systems appear in one figure. Moreover, the size of print in the tables varies, suggesting that the presentation is derived directly from a lantern slide. Finally, it was presumably an editorial decision to use bold type for certain words and statements in the text. These appear like statements made by some drug house representatives.

Although it is interesting and informative in part, this is not a book which this reviewer would recommend for his hospital library.

J. M. Reid

The Physiology of Breathing: A Textbook for Medical Students. By Arend Bouhuys. Published (1977, paperback) by Academic Press. Pp. 352; indexed; illustrated. Price £8.85.

Those prepared to work carefully through lucid, tightly packed prose and clearly annotated graphical presentations will find this a very rewarding book. It is a book to refer to for clarification both of the background and of the current state of the art in each subsection of respiratory physiology. It is probably not a book by which to be first introduced to the subject and so not, in Britain at any rate, a book which medical students are likely to use, except for the few whose interest is particularly captured by the physiology of breathing. For a medical graduate embarking on a respiratory research project or a study of the topic in relation to aspects of anaesthesia or pulmonary dysfunction it would be ideal. The sub-title "A textbook for medical students" is thus misleading. Although of very manageable size and readability it is more in the nature of a scholarly review with extensive references (60, for example, for Pressure–Flow Relations). One expects Professor Bouhuys, as an expert in the field of mechanics of breathing, to write well on this, but his section on control, for instance, is at least as good: there is a commendable—and comprehensible—summary concerning the brain-stem "centres", which relates recent functional and anatomical studies to the classical and modern models of the system. Some sections seem more difficult than others; the reader wishing to understand ventilation–perfusion ratios, for example, would perhaps be discouraged and better advised first to look elsewhere—such as West's book—to grasp what it is all about; then to come to Bouhuys' account and appreciate its logicality and completeness.

This is an intellectually satisfying book, but it is not by any means "academic" in the pejorative sense; there is an eye open to practical application and to the potential growth of clinical importance, even whilst the author is guiding us over the most stony theoretical ground.

The summaries at the end of each chapter are masterpieces of précis; they alone could provide a brisk and comprehensive revision of the whole field as well as pointers to areas of clinical application and of current research.

Sheila Jennett

Pain Control in Obstetrics. By Ezzat Abouleish. Published (1977) by J. B. Lippincott, Philadelphia and Toronto. Pp. 452; illustrated; indexed. Price £22.

Although the title does not describe this book as a text of local anaesthetic techniques in obstetrics, this is the subject in which it excels. Dr Abouleish's interests in obstetrics are reflected in the choice of subject matter, and are slightly unusual. The first of the three sections of the book considers maternal anatomy and physiology, with a good account of placental function and placental drug transfer. The pharmacology of local anaesthetic agents is considered in some detail, as is the physiological effect of "vertebral" blocks. An extensive account of vomiting aspiration and regurgitation follows and a lengthy chapter on amniotic fluid embolism. The section ends with a useful discussion of the assessment of fetal wellbeing antenatally and during labour.

The second section is directed to a detailed and practical account of the techniques of regional anaesthesia which are employed by anaesthetists in the U.S.A. Each technique is considered separately and includes history, anatomy, physiology, choice of drugs, indication and contraindication. A clear description, amplified by excellent diagrams is given of Dr Abouleish's own method of choice in performing the blocks. Complications and their management are discussed in excellent detail. By considering such techniques in this way, much repetition occurs, but it has the advantage of encouraging easy reference. Each chapter is complemented by an outstandingly complete and up-to-date list of references. Dr Abouleish's experience and enthusiasm are clearly evident; emphasis is placed on his preference for regional anaesthetic techniques which is reinforced by the very brief but adequate chapter on general anaesthesia. Envy is generated at the choice of drugs available in the U.S.A. which are not available in the United Kingdom, for example 2-chloroprocaine, bupivacaine 0.75%, spinal amethocaine and lignocaine.

The final section considers neonatal resuscitation, the design of a neonatal intensive care unit and postpartum sterilization.

The value of this book lies in the excellent account of local anaesthetic techniques, the weakness in the absence of information on aspects of obstetric care. There is, for example, only passing reference to analgesic drugs, other than local anaesthetic agents and almost no information about maternal disease and its management. This renders the book less than complete. The volume is beautifully produced but unfortunately very expensive.

J. THORBURN

Anesthesia in Obstetrics. Maternal, Fetal and Neonatal Aspects. By George A. Albright. Published (1978) by Addison-Wesley Publishing Company. Pp. 480; illustrated; indexed. Price £31.50.

In the past few years there has been a marked and welcome increase in interest in obstetric anaesthesia and related matters on both sides of the Atlantic. This is demonstrated by the large numbers who attend meetings on the subject. It is not surprising, therefore, that a new American book has appeared with the stated aim of "presenting a comprehensive, up-to-date, readable source of information on the essential aspects of obstetric anesthesia care".

The book is divided into six sections, each containing several chapters. The first is a general introduction with discussion of anaesthetic morbidity, maternal mortality and evaluation of the obstetric patient before operation. The second section describes the physiological changes occurring during pregnancy and labour, but also contains details of pelvimetry, different types of forceps and the vacuum extractor, which most British anaesthetists would consider out of place in a textbook on obstetric anaesthesia. Although the second section is entitled "Physiology and Pharmacology", only local anaesthetic agents are discussed. This is done lucidly and in some detail, but an unfortunate error in figure 5-7 would make the understanding of the effect of fetal acidosis on placental transfer of local anaesthetics rather difficult for those not already well versed with the subject. Also in this chapter is a detailed description of how to use a laryngoscope and pass a tracheal tube!

The third section deals with analgesia and anaesthesia for labour and delivery and contains chapters on psychoanalgesia, systemically administered drugs and the inhalation agents. The technique described of administering the latter would not be approved by most British anaesthetists, but it is a relief to see that the author condemns the practice of using inhalation anaesthesia with a face mask for delivery, which one gathers is still not uncommon in the United States.

Section four concerns major regional anaesthesia, and following a chapter on fundamental considerations, there are chapters on spinal, extradural and caudal anaesthesia. This is the best section of the book, with all aspects of the various techniques discussed clearly and in detail. The illustrations, as they are throughout, are excellent and undoubtedly add to the astonishing cost of the book.

Section five discusses maternal complications and opens with a chapter on Caesarean section and emergency delivery. The various methods of local and general anaesthesia are considered, the pros and cons of each being clearly presented. The following two chapters, however, on maternal health and obstetric complications, again contain much that most anaesthetists in this country would consider out of place in such a book. Similarly, the final section of the book, dealing with the fetus and neonate, presents much information which is really outside the province of the anaesthetist.

Many of the above comments should not be regarded as criticism, but rather as a reflection of the difference in attitude and outlook of British and American anaesthetists. It would appear that the latter are expected to know considerably more detail of operative obstetrics, fetal development *et cetera* than their British counterparts, and expect to find such information in a book such as this. A British anaesthetist seeking to advance his knowledge of the pharmacokinetics of local anaesthetics or uptake and distribution of inhalation agents would not turn to a textbook on obstetric anaesthesia.

There are few serious criticisms, but they are extremely important and deal mainly with one aspect. Inhalation of gastric contents is probably the single most important subject in obstetric anaesthesia, yet in this book the subject receives scant attention. The effects of pregnancy and labour on gastric function are not discussed in the chapter on physiology of pregnancy. There is no mention of the alterations in intragastric pressure brought about by drugs or changes in posture, and the factors affecting the opening pressure of the gastro-oesophageal sphincter are ignored. It has been shown clearly that magnesium trisilicate mixture must be taken 2-hourly and not every 3-4 h as recommended here. While agreeing with the author that passage of a nasogastric tube is unpleasant and does not guarantee an empty stomach, one cannot agree that induction of vomiting with apomorphine is potentially dangerous and even more unpleasant. There is no evidence for the former, while the latter has been shown to be untrue.

Apart from the above criticisms, this book fulfils its stated aims, certainly from the point of view of our American colleagues. In fairness, however, it should be pointed out that there are two excellent British textbooks on this subject at considerably less cost.

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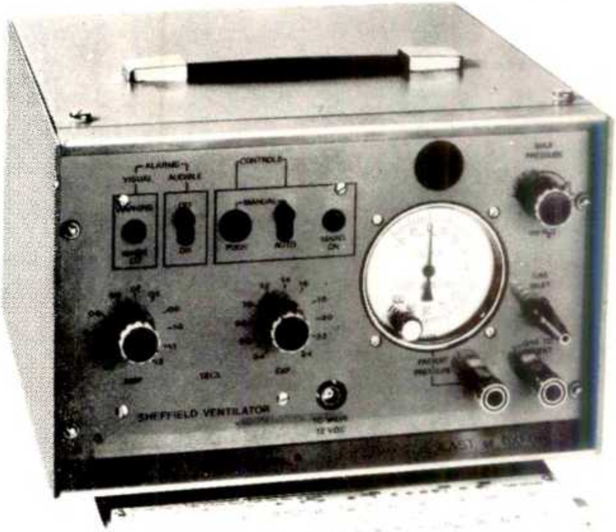

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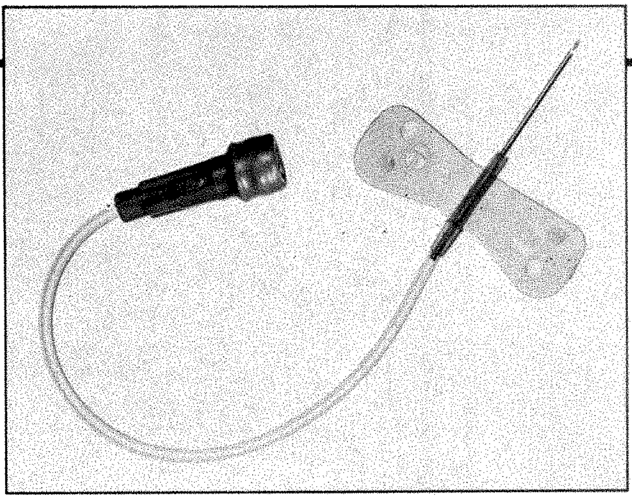

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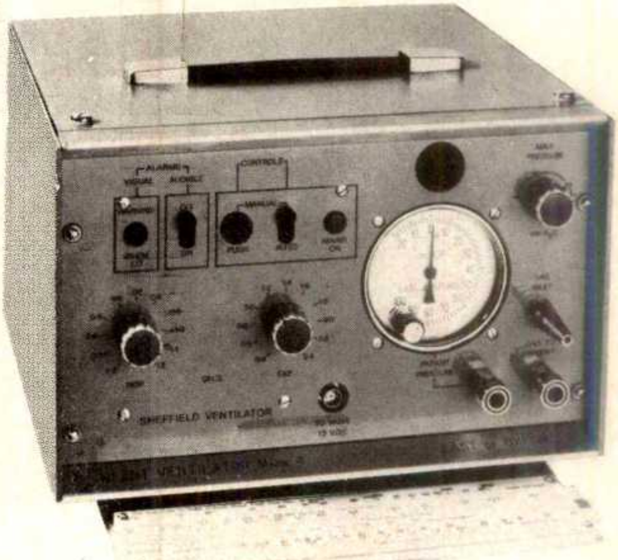

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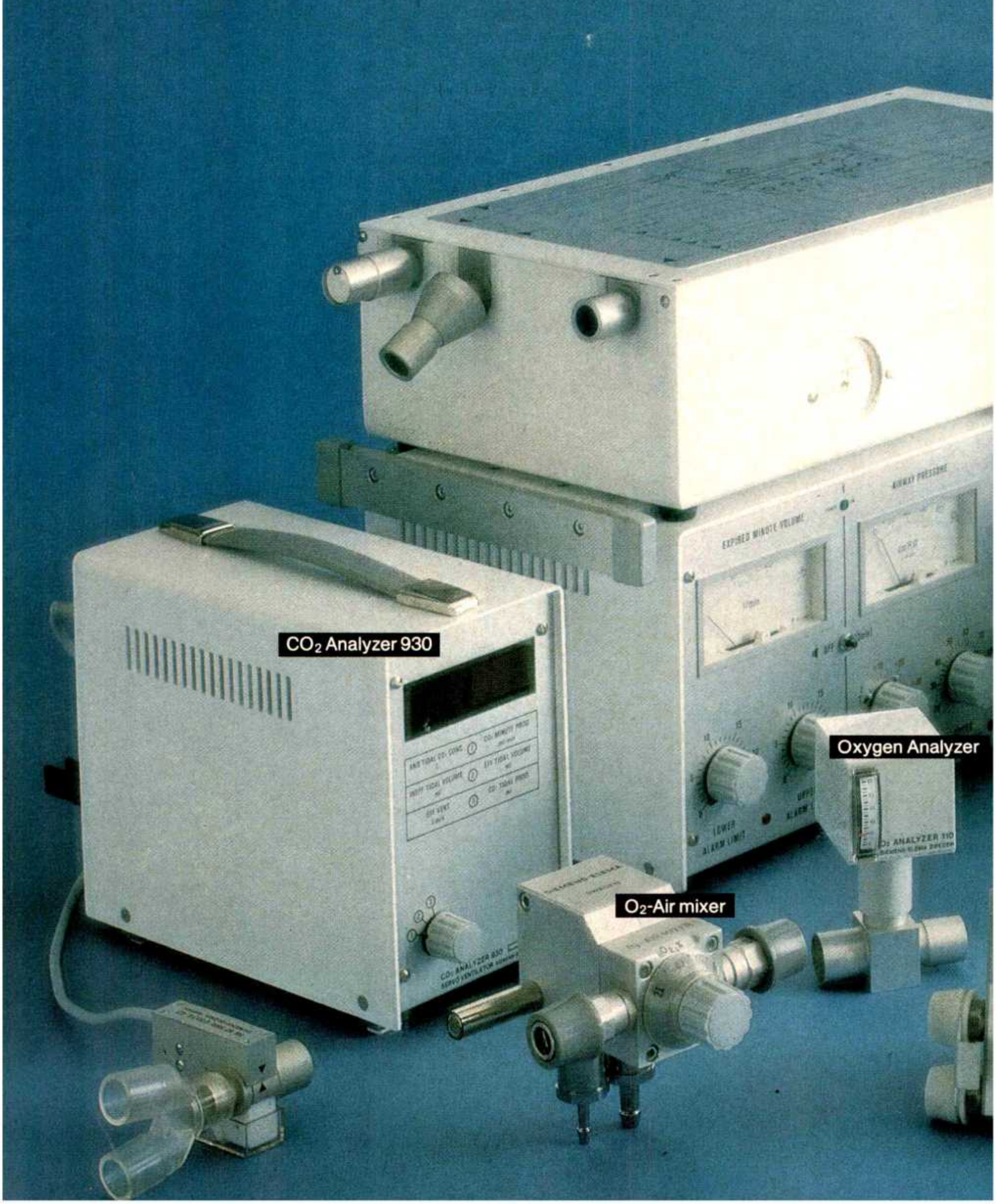

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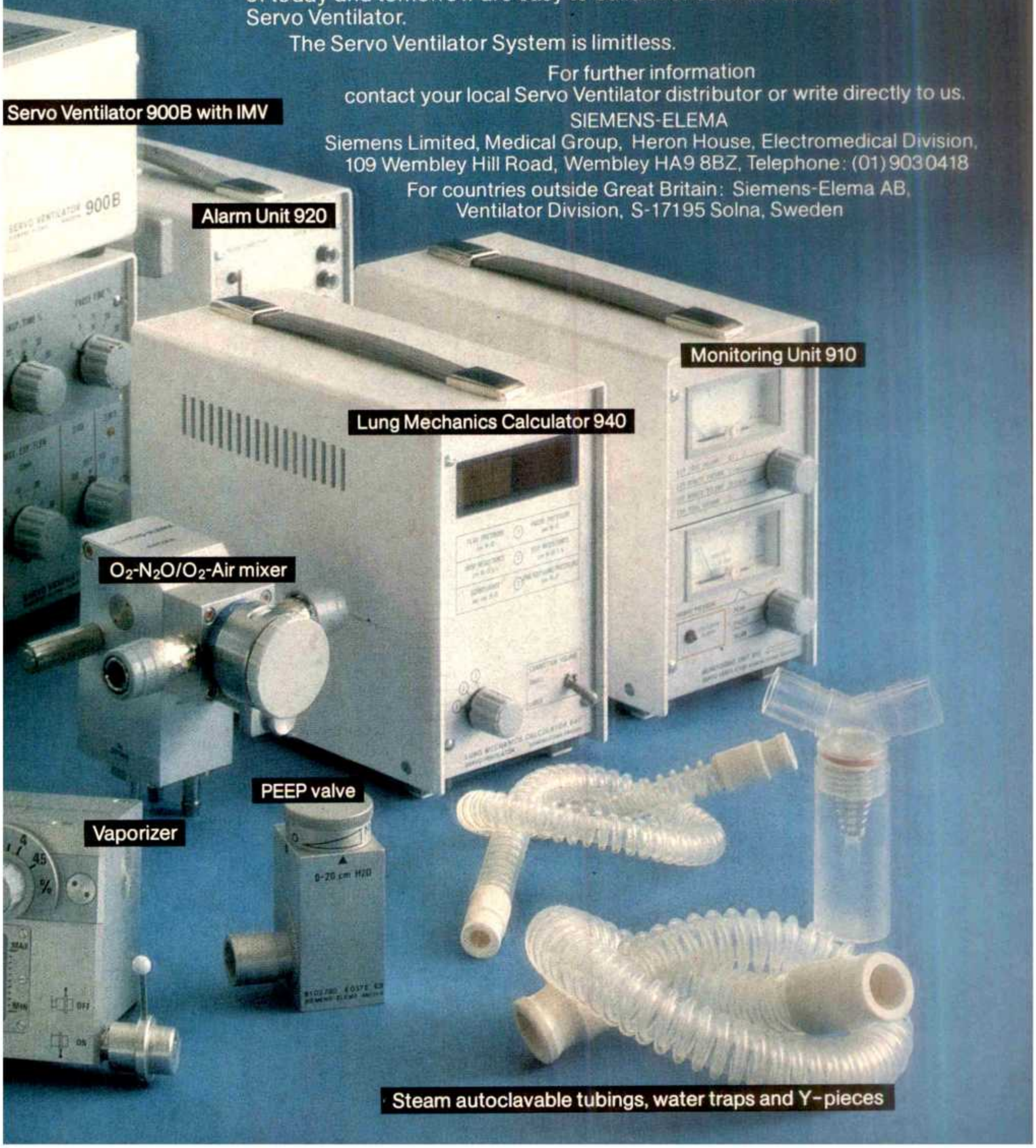
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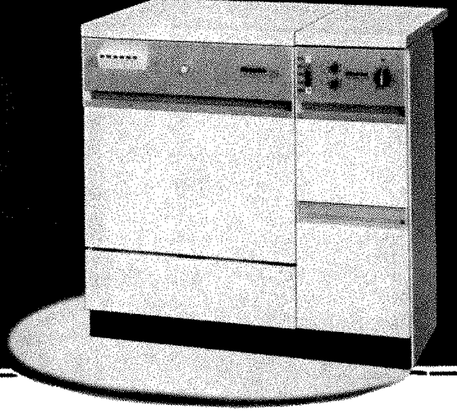

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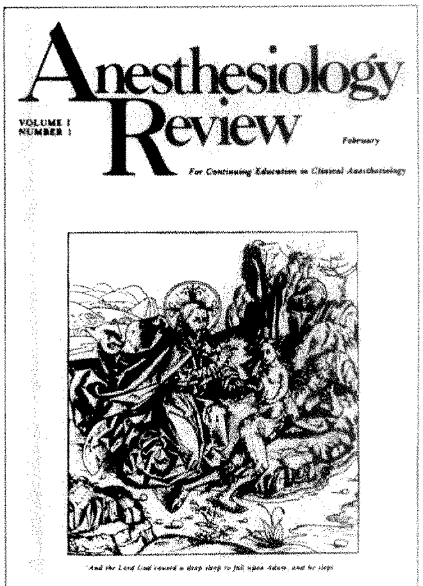

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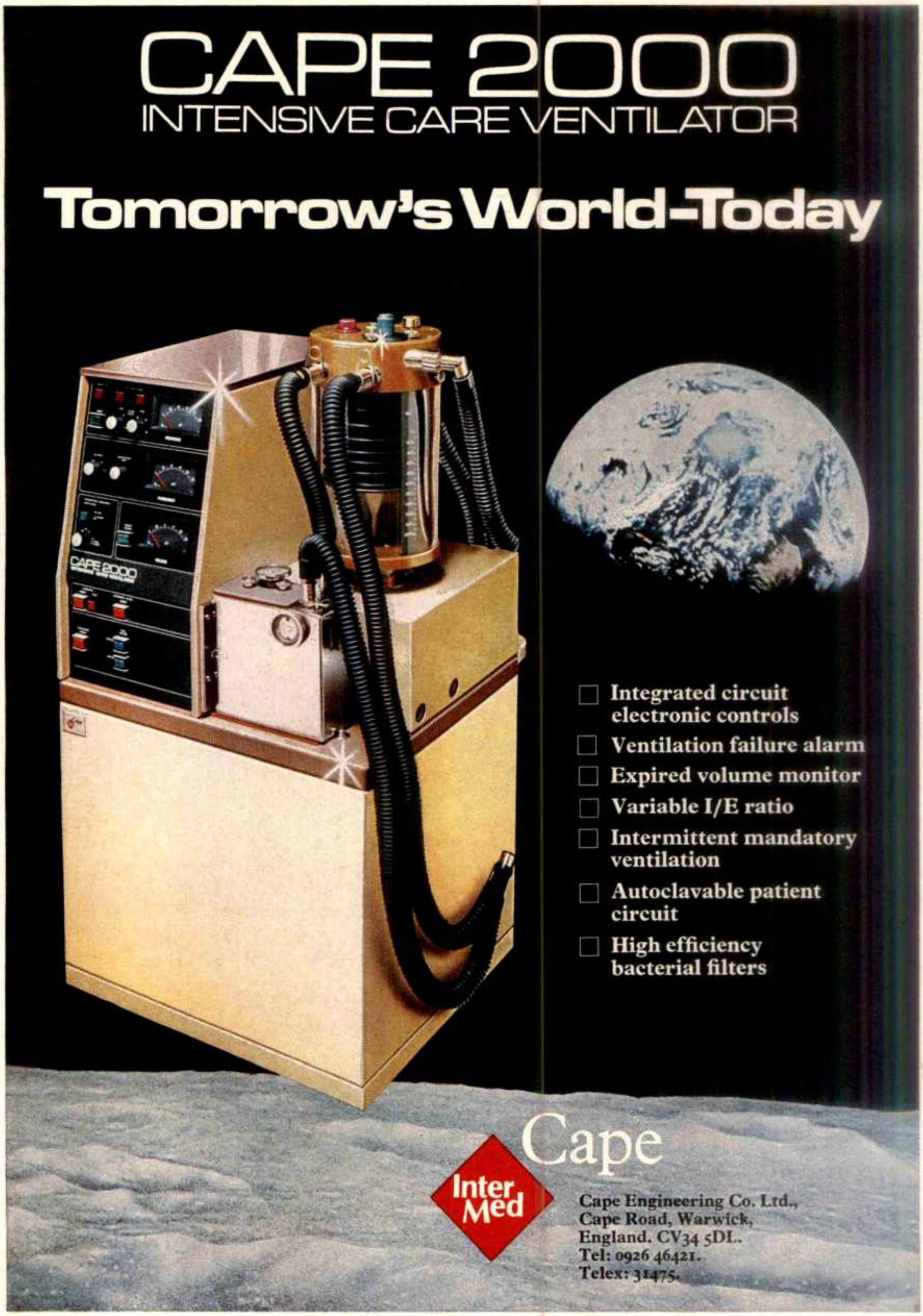

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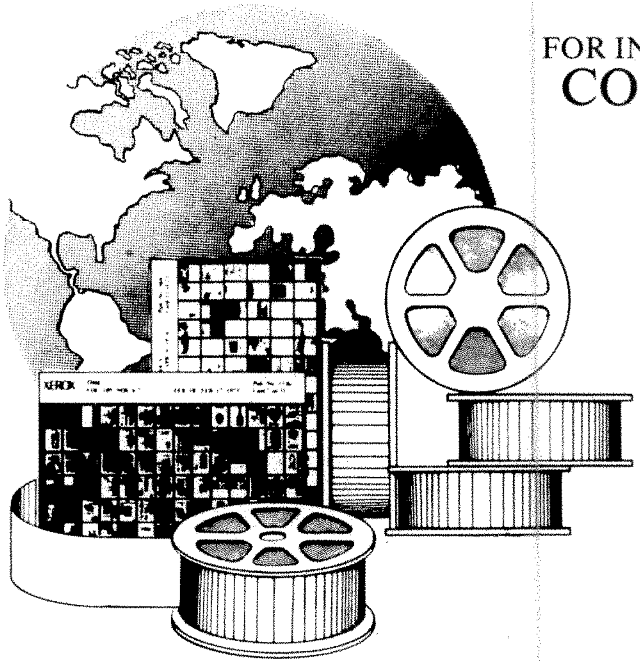

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Der *Anaesthesist*

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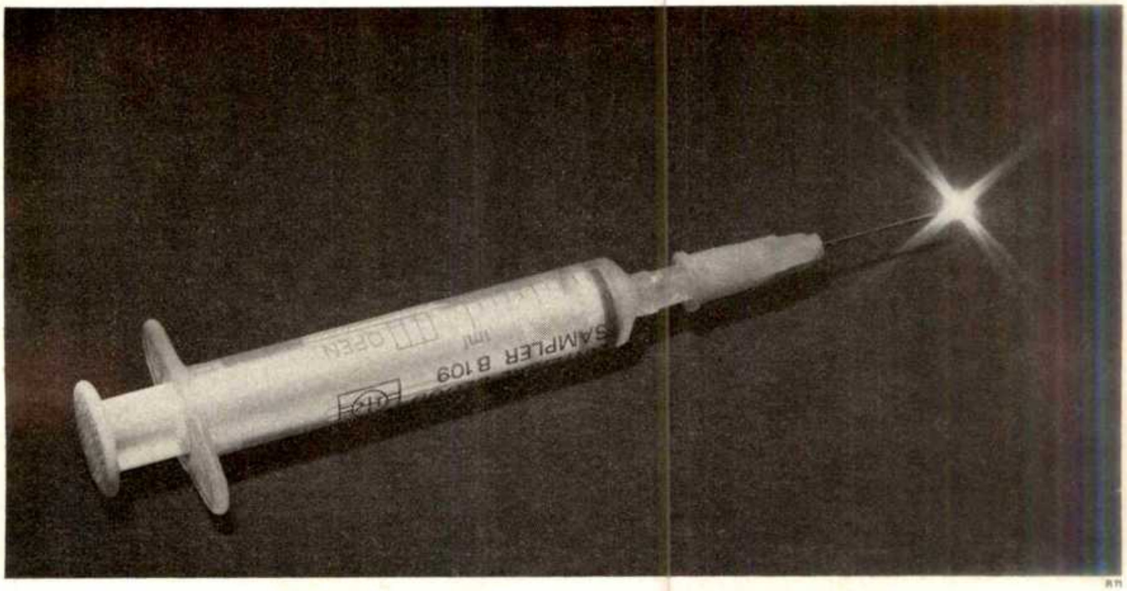

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BRITISH JOURNAL OF ANAESTHESIA

VOLUME 51, No. 2 FEBRUARY 1979

EDITORIAL

EXTRADURAL ANALGESIA FOR CAESAREAN SECTION

Subarachnoid analgesia has had a long, sometimes chequered, history as an anaesthetic for Caesarean section. Death associated with the technique was formerly attributed to ventilatory inadequacy as the result of upward pressure of the gravid uterus upon the diaphragm or was classed as "unexplained". These deaths were almost certainly a result of hypovolaemia, caval occlusion and arterial hypotension and should no longer occur with any form of spinal analgesia. Nevertheless, for some anaesthetists, the shadow cast by such deaths persists and subarachnoid and extradural analgesia are feared for obstetric surgery. This fear is more difficult to justify in the light of current understanding of the mechanisms of circulatory failure during conduction analgesia in the obstetric patient.

In the U.S.A. subarachnoid analgesia has never fallen out of favour for obstetric use, although it is being superseded by extradural analgesia in teaching centres (Hicks, Levinson and Shnider, 1976); extradural techniques are used quite extensively in Canada, Australia, South Africa and elsewhere. Within the past 2 or 3 years there has been an upsurge of interest in extradural analgesia for Caesarean section in Great Britain and there are now centres in which 50–70% of sections are performed under extradural block.

The reasons for this development include (a) greater awareness of the hazards of general anaesthesia in obstetrics and in particular of the risk of death from Mendelsohn's syndrome, hypoxia or failed intubation; (b) understanding of the need to avoid aorto-caval occlusion by the use of a left lateral tilt and to maintain blood volume by pre-loading with a balanced salt solution; (c) the demonstration by neurobehavioural studies that the more subtle depressant effects of general anaesthetics persist in the neonate for up to 48 h in addition to the immediate effect in delaying the onset of spontaneous ventilation in some infants; (d) the availability of powerful, longer-acting local analgesic agents, such as bupivacaine and etidocaine, of which the fetal/maternal concentration ratios are low; (e) the wish of many mothers to participate actively in the birth of their children; (f) the alert and pain-free condition of the mother in the period immediately after operation; (g) circumvention of the problem of awareness during general anaesthesia; (h) the growth of obstetric anaesthesia as a sub-specialty with the provision of a resident anaesthetist in more obstetric units and the allocation of more consultant sessions to obstetric anaesthesia, and (i) the satisfaction which all in attendance, even the most case-hardened anaesthetist, can gain from sharing in the mother's joy as she holds her infant while oblivious to the continuing surgery.

Many anaesthetists doubt the adequacy of extradural analgesia for intra-abdominal surgery in the conscious, unsedated patient. Pain requiring supplementary i.v. injections of methohexitone, Althesin, narcotic analgesics or even a full general anaesthetic can occur in up to 20% of patients undergoing Caesarean section or abdominal hysterectomy under extradural analgesia (Milne and Murray Lawson, 1973; Bridenbaugh et al., 1976) and the anaesthetist must always be prepared to treat pain immediately and effectively. If the undoubted benefits of extradural analgesia are to be fully exploited for Caesarean section, then it is important that the percentage of imperfect blocks be greatly reduced.

Intrapelvic structures receive some of their sensory innervation from sacral nerve roots and a block which allows painless incision of the abdominal wall may not eliminate the pain caused by traction upon the uterus or bladder. Sacral nerve roots may be especially difficult to block because their diameter is greater; in a series of non-obstetric patients the first sacral nerve roots were not blocked in 17.5% of cases (Galindo et al., 1975). Subcostal discomfort in the later stages of the operation may be a result of the upward tracking of blood within the abdominal cavity and shoulder-tip pain is occasionally experienced, probably a result of the presence of air or blood under the diaphragm. With careful surgical technique and the use of a large volume of 0.5% bupivacaine to ensure blocking of all nerve roots from S4 to T8 or higher, it has been found possible to reduce the frequency of pain to 3% (Thorburn and Moir, 1978). A first extradural injection of 10 ml 0.5% bupivacaine was given in the sitting position and this position was maintained for 15 min to encourage downward spread. A further 8–16 ml was then injected, sometimes in divided doses, with the patient in the horizontal position with left lateral tilt. Surgery commenced only when cutaneous analgesia extended from S4 to T8 or higher. Similar quantities of bupivacaine have been found to leave the neonate clinically unaffected and to produce acceptable concentrations of the drug in maternal, fetal and neonatal blood (Magno, 1976). Other suitable solutions are 1% etidocaine (Lund et al., 1977) and 0.75% bupivacaine where available. This technique is effective but time-consuming.

Other important points of technique include the infusion of 1000 ml of a balanced salt solution before operation (Wollman and Marx, 1968) and the use of a left lateral tilt (Buley et al., 1977). In these circumstances placental blood flow should be well maintained and fetal accidosis should be minimal and certainly no greater than that which occurs with general anaesthesia (Wallis et al., 1976; James et al., 1977; Jouppila et al., 1978). The great majority of infants will establish spontaneous respiration within 30 s (Thorburn and Moir, in preparation).

If an i.v. injection of ergometrine is given at operative delivery under extradural analgesia then retching or vomiting occur in more than 40% of patients (Milne and Murray Lawson, 1973; Moodie and Moir, 1976). Ergometrine should be replaced by an i.v. injection of 5 or 10 units of oxytocin and this should be followed by an infusion of oxytocin 20 units in 500 ml of fluid. If hypovolaemia is prevented the transient vasodilator action of oxytocin is unlikely to cause arterial hypotension, and vomiting resulting from uterine traction is rare if sacral nerves are blocked adequately (Thorburn and Moir, in preparation).

Highly motivated women will happily accept the discomforts and the mental stress of Caesarean section under extradural analgesia and will almost always express a desire to have this form of anaesthesia for any future operative delivery. Extradural analgesia should never be forced upon a truly unwilling mother. Where delivery is urgent there may be insufficient time for the production of an adequate block and general anaesthesia will then be preferred. In a hospital in which extradural analgesia is used regularly for Caesarean section it is possible to offer a choice of anaesthetic to most mothers. Mothers can be informed of this possibility during pregnancy and where elective section is decided upon, the choice of anaesthetic can be discussed. The margin between success and failure is slight. Adequate expertise, attention to detail, sufficient time and a sympathetic approach are essential. Perhaps the wider use of extradural analgesia for Caesarean section may yet reduce the number of maternal deaths attributable to anaesthesia. It would be tragic if careless or inexpert use of extradural analgesia were only to replace deaths from Mendelson's syndrome and failed intubation with deaths from acute circulatory failure.

Donald D. Moir

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SOME PHYSIOLOGICAL AND METABOLIC EFFECTS OF SODIUM NITROPRUSSIDE AND CYANIDE IN THE DOG

P. J. SIMPSON, L. ADAMS, C. J. VESEY AND P. COLE

SUMMARY

The cardiovascular and acid–base changes following equivalent i.v. bolus doses of sodium nitroprusside (SNP) and potassium cyanide (KCN) have been studied in two groups of anaesthetized dogs. In a third group, the metabolic changes produced by i.v. infusion of SNP 1.5 mg kg^{-1} at a constant rate over 1 h have been studied. In contrast to a decrease in arterial pressure following SNP, hypertension and tachycardia occurred after the administration of KCN, with hyperventilation and an increase in packed cell volume. During infusion of SNP, increases in plasma cyanide concentrations were associated with an increase in arterial base deficit, plasma lactate and excess lactate and a decrease in oxygen consumption. The occurrence of lactic acidosis with SNP 1.5 mg kg^{-1} suggests that this may be the maximum safe dose for short term infusion. However, all these changes reversed spontaneously following discontinuation of SNP, indicating that base deficit is an adequate metabolic monitor during administration of SNP.

The cardiovascular changes associated with i.v. sodium nitroprusside (SNP) have been well documented (Schlant, Tsagaris and Robertson, 1962; Ross and Cole, 1973; Wildsmith et al., 1973; Adams et al., 1974; Wang, Liu and Katz, 1977). Similarly, the effects of the drug on acid–base and blood-gas measurements have been studied in man (Wildsmith, Drummond and MacRae, 1975). Although the toxicity of nitroprusside has been ascribed to cyanide (Vesey and Cole, 1975), the contribution of this breakdown product to the hypotensive action of the drug has not been investigated. Indeed, there is some evidence that cyanide itself can produce various cardiovascular effects (Krasney, 1971; Barcroft, 1973; Liang and Huckabee, 1973) and increased cyanide concentrations resulting from abnormalities in its metabolism have been implicated as a possible cause of resistance to the hypotensive action of SNP (Davies et al., 1975a; Tremblay et al., 1977).

We have studied in dogs the cardiovascular effects of i.v. bolus injections of SNP and of an equivalent dose of potassium cyanide (KCN) and have recorded the changes produced in the blood-gas and acid–base state. Similarly, we have investigated the changes following i.v. infusion of SNP 1.5 mg kg^{-1}, our recommended maximum dose for man (Vesey, Cole and Simpson, 1975, 1976), at a constant rate over 1 h, to determine if this is free from evidence of cyanide toxicity (Simpson, 1978).

Since cyanide is associated with the development of histotoxic hypoxia, an attempt has been made to assess the adequacy of tissue oxygenation during nitroprusside infusion. The development of a progressive and irreversible metabolic acidosis has been recorded in several fatalities associated with i.v. SNP (Jack, 1974; Merrifield and Blundell, 1974; Davies et al., 1975b), and it is probable that the histotoxic effect of cyanide, producing an excess of lactate, is responsible for this acidosis. Measurements of plasma lactate and pyruvate have been carried out therefore, both during and after infusion of SNP and excess lactate has been derived subsequently from these results (using the formula of Huckabee (1958)). The simultaneous changes in oxygen consumption have been studied also, since this value would be expected to decrease during a hypoxic episode. The relationships of these variables to arterial base deficit have been examined to determine if measurement of the latter would provide a reliable indication of the development of SNP toxicity.

METHODS

The methods used have been described in detail elsewhere (Vesey et al., 1979). At the time intervals

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indicated, samples of mixed venous and arterial blood were obtained from the pulmonary and superficial femoral arteries. The samples were analysed immediately for pH, $P\text{CO}_2$, $P\text{O}_2$ (Instrumentation Laboratories 413 blood-gas analyser) and oxygen content (Lexington Instruments Lex-O_2-Con). Measurements of haemoglobin (cyanmethaemoglobin technique) and packed cell volume (microhaematocrit method) were made on all samples. Base excess or deficit was calculated from the values of pH and $P\text{CO}_2$.

Plasma lactate and pyruvate estimations were carried out using commercially available enzymatic test combinations (Boehringer Corporation) and excess lactate was calculated from these results. Blood samples were withdrawn into precooled syringes, separated immediately at 0 °C in a refrigerated centrifuge and an aliquot of the plasma added to perchloric acid 0.6 mol litre^{-1}. The mixture was centrifuged, the supernatant stored at 4 °C and the lactate determined within 24 h.

In all three groups of dogs, simultaneous recordings of arterial pressure and heart rate were accompanied by measurement of central venous pressure (CVP) (groups 1 and 2) or pulmonary artery pressure using a Swan–Ganz catheter (group 3). In groups 1 and 2, oxygen consumption was measured directly (Douglas bag technique) and cardiac output determined from the arterio–venous oxygen difference using the Fick principle. In group 3, cardiac output was measured by dye dilution using indocyanine green, and oxygen consumption was derived.

Measurements of oxygen consumption, cardiac output and plasma lactate were made in only three dogs in each of groups 1 and 2, but in all animals in group 3.

RESULTS

The mean concentrations of plasma and red cell cyanide and plasma thiocyanate, recorded in the three groups of dogs, have been discussed by Vesey and others (1979). Figure 1 shows arterial hypotension following administration of SNP both as a bolus dose (group 1) and as an infusion (group 3); potassium cyanide (KCN), on the other hand, resulted in a transient increase in arterial pressure. There was a sudden increase in CVP following the administration of KCN, but a minimal increase following SNP (fig. 2). This increase was associated with marked spontaneous hyperventilation (a normal response to KCN, since the dogs were not paralysed) and a corresponding reduction in the otherwise steady value of Pa_{CO_2}.

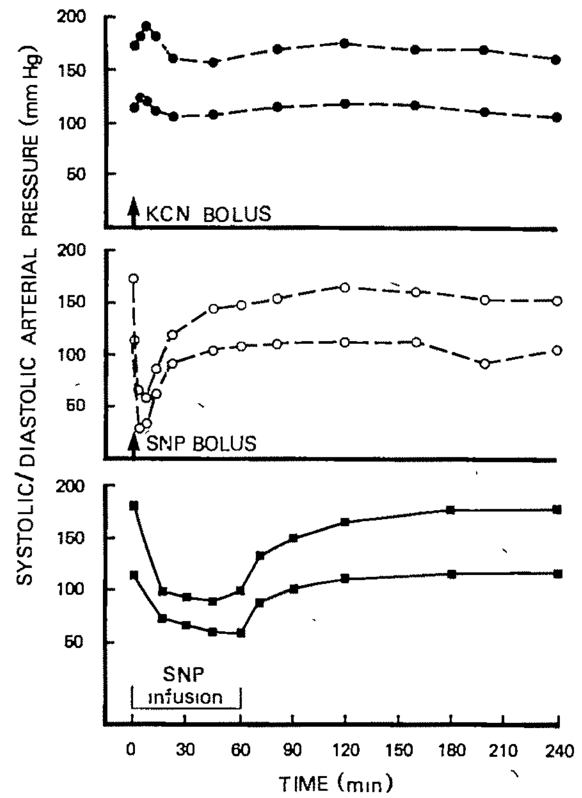

FIG. 1. Systemic arterial pressure (mean) in all three groups of dogs.

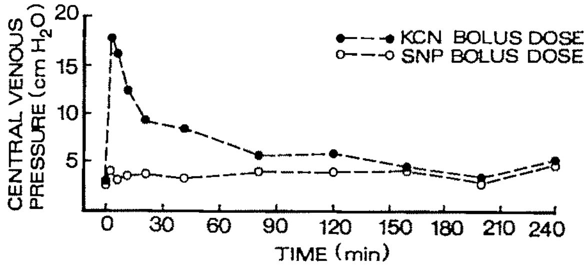

FIG. 2. Mean central venous pressure in groups 1 and 2.

In group 3, pulmonary artery pressure decreased in parallel with systemic pressure, and these changes were sustained during the period of infusion of SNP. Bolus injections of both SNP and KCN produced changes in heart rate (fig. 3); infusion of SNP resulted in a smaller increase, which was maintained throughout the period of infusion. However comparisons between the groups are complicated by differences in baseline values. Slight increases in cardiac output occurred following administration of

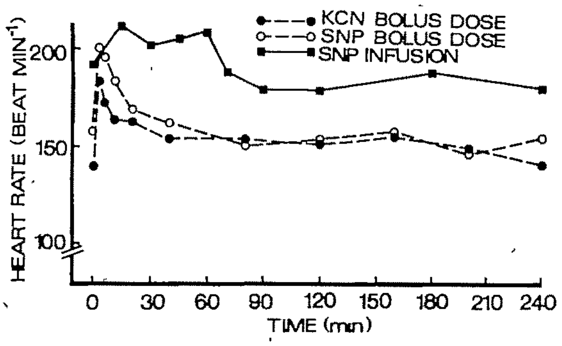

FIG. 3. Mean heart rate in all three groups of dogs.

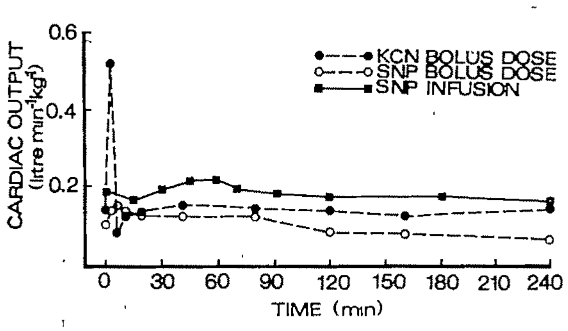

FIG. 4. Mean cardiac output in all three groups of dogs. In groups 1 and 2, measurement of cardiac output was made using the direct Fick principle, while in group 3, dye dilution with indocyanine green was used.

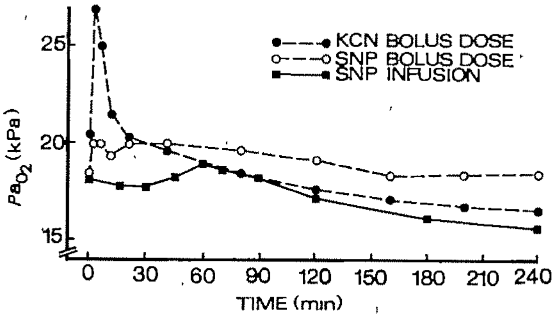

FIG. 5. Mean values of arterial P_{O_2} in all three groups.

SNP, both as a bolus dose and during infusion (fig. 4); in contrast, KCN produced a very large, but transient, increase in cardiac output although the validity of the Fick principle in such rapidly changing circumstances must be considered doubtful.

Although a significant increase in Pa_{O_2} was observed following KCN (group 2) little change occurred following SNP (groups 1 and 3) (fig. 5). Although oxygen consumption was estimated in only three dogs from each of groups 1 and 2, those receiving potassium cyanide exhibited a decrease to approximately 50% of the initial value within 5 min of administration, followed by a rapid return to normal values. However, the results of oxygen consumption measurements in group 1 were inconclusive. The dogs in groups 1 and 2 showed an increase in plasma lactate, which returned subsequently to baseline values. The peak concentrations occurred later in the SNP group (20–40 min after administration) than in the KCN group (5–10 min). However, the dogs receiving SNP demonstrated only a 2–3-fold increase in lactate concentrations, in contrast to a 5–9-fold increase in the cyanide group. Pyruvate was not measured in group 1 or 2, precluding the calculation of excess lactate. The development of lactic acidosis in each of these two groups coincided, as might be expected, with an increase in arterial base deficit. The magnitude of the metabolic acidosis was related to the lactate concentrations observed; thus the KCN group developed a maximum base deficit of 7.3 ± 1.65 mmol litre^{-1} (mean ± SEM) and a peak increase in plasma lactate of 6.9 ± 1.3 mmol litre^{-1}, compared with 2.5 ± 0.75 and 1.95 ± 0.49 mmol litre^{-1} respectively in the SNP group.

A more comprehensive study of tissue oxygenation was carried out in the dogs in group 3. The relationship between plasma lactate and arterial base deficit, both during and after SNP infusion, is shown in figure 6 and regression analysis confirms a close correlation between these two variables ($r = 0.95$; $P < 0.001$). The two measurements most likely to indicate inadequate tissue oxygenation (excess lactate and oxygen consumption) are shown together in figure 7. A decrease in oxygen consumption was associated with an increase in excess lactate ($P < 0.01$ for excess lactate and $P < 0.02$ for oxygen consumption), both changes occurring during the infusion of SNP.

Both KCN and, to a lesser extent, SNP produced an increase in PCV (maximum increases above basal = 24.9 ± 4.13% and 9.1 ± 1.7%, mean ± SEM, both 5 min after the bolus dose) although there was no statistically significant increase in the SNP group.

DISCUSSION

The cardiovascular responses to SNP were similar to those reported previously (Adams et al., 1974). The hypotensive action of SNP was not associated with high concentrations of plasma cyanide, since the hypotension occurred more rapidly than the increase in plasma cyanide in groups 1 and 3.

The effect of SNP on cardiac output in dogs is not

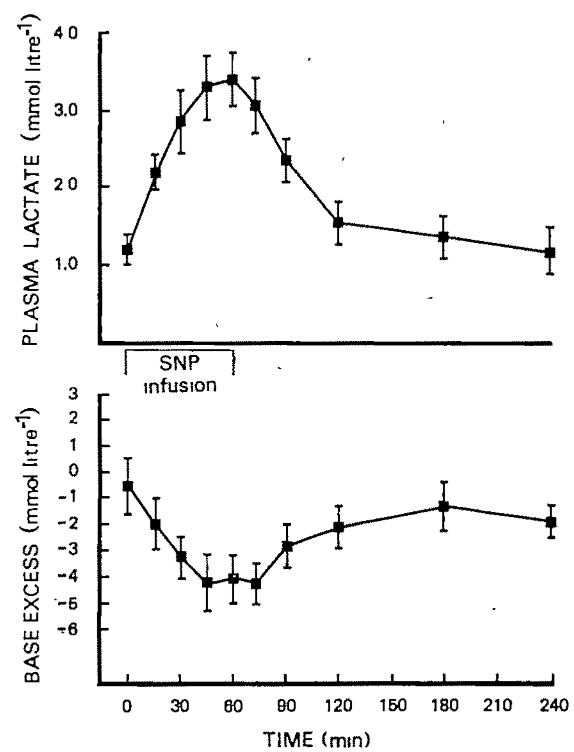

FIG. 6. Simultaneous mean values of arterial base excess and plasma lactate, both during and after infusion of SNP in group 3.

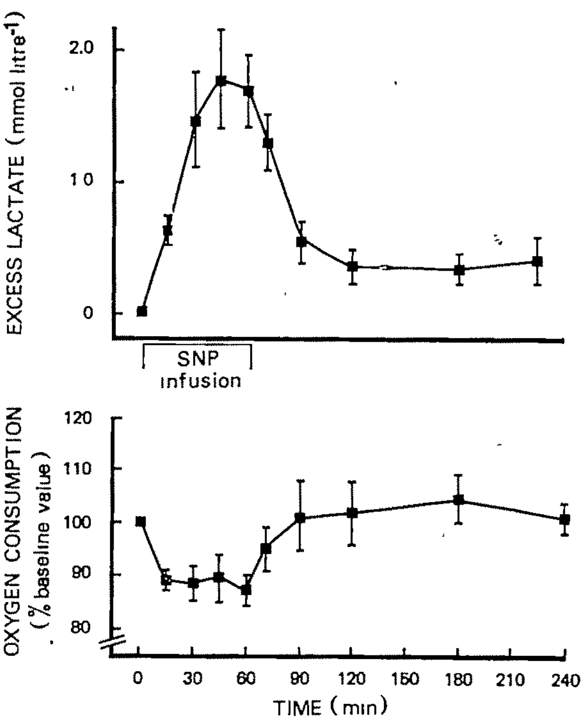

FIG. 7. Simultaneous mean values of plasma excess lactate and the percentage change in oxygen consumption, both during and after infusion of SNP in group 3.

as well defined as its hypotensive action. Ross and Cole (1973) demonstrated significant increases in cardiac output following infusion of SNP, whereas Adams and colleagues (1974) were unable to demonstrate any change under various anaesthetic conditions. More recently, both Wang, Liu and Katz (1977) and Michenfelder and Theye (1977) have shown that a significant decrease in cardiac output occurs following infusion of SNP. The results of the present study show that cardiac output increases following SNP, both as a bolus dose and as an infusion, although these changes are not statistically significant.

However, the dogs in group 3 appear to be in two distinct categories: in five, cardiac output was increased, while in the remainder it was decreased slightly or unchanged. Similarly, McDowall and his colleagues (1974) grouped their baboons depending upon the response to SNP. These results may be dependent upon individual variation and may, in part, explain the conflicting results of previous studies. Similar variations have been reported in studies in conscious man (Schlant, Tsagaris and Robertson, 1962; Franciosa et al., 1972). It is also possible that variation in cardiovascular response may result from the anaesthetic technique used; while Ross and Cole (1973) used urethane, other workers have used a variety of agents, including pentobarbitone, halothane and in particular nitrous oxide, which have cardiovascular effects of their own.

In those animals in which cardiac output increased it is noteworthy that this occurred after 45–60 min of infusion of SNP, suggesting that haemodynamic values do not stabilize as early as 2 min after commencement of infusion as stated previously (Adams et al., 1974). The very large, although transient, changes in cardiac output following injection of KCN confirm the findings of Liang and Huckabee (1973) and one may speculate that increases following administration of SNP may be mediated by cyanide, particularly since the increase in cardiac output after 45 min coincided with the maximum plasma HCN concentration. The well-documented increase in heart rate in response to SNP is evident from this study, but although cyanide itself produced a marked tachycardia this may not explain the effect of nitroprusside since changes occurred very rapidly. A decrease in stroke volume in all the dogs receiving SNP confirmed the findings of Adams and his colleagues (1974) and contrasted with the increase associated with the administration of cyanide.

The large increase in central venous pressure in the dogs receiving KCN was undoubtedly a result of the marked spontaneous hyperventilation and straining against the ventilator observed in these animals, a response to cyanide which is well documented (Krasney, 1971; Levine, 1975). This also explains the increase in Pa_{O_2} and the reduction in Pa_{CO_2} recorded in this group. The failure to demonstrate a significant reduction in Pa_{O_2} in either of the two groups of dogs receiving SNP is surprising in view of the findings of other workers, but this may be because the dog was lying in the lateral position during the study. Wildsmith, Drummond and MacRae (1975) noted a significant decrease in Pa_{O_2} in man and recommended an increase in inspired oxygen during the period of hypotension, and Adams and colleagues (1974) reported similar small decreases in dogs.

The large packed cell volumes in groups 1 and 2 were associated with large concentrations of plasma cyanide and may be a response to this. Increases in haematocrit or haemoglobin concentration as a result of hypoxia from rebreathing (Kramer and Luft, 1951) or infusion of cyanide (Liang and Huckabee, 1973) in the dog have been shown to result from release of splenic stores of red blood cells.

It would appear from the reported fatalities (Jack, 1974; Merrifield and Blundell, 1974; Davies et al., 1975b) that the toxicity of SNP is essentially a result of progressive and ultimately irreversible metabolic acidosis indistinguishable clinically from cyanide poisoning. We have stated elsewhere that 1.5 mg kg^{-1} should be the maximum dose of sodium nitroprusside which may be administered over a short period (Vesey, Cole and Simpson, 1975, 1976). This dose, administered at a constant rate over 1 h to the dogs in group 3, produced increases in plasma lactate, which were associated with a maximum increase in arterial base deficit of 3.75 mmol litre^{-1}.

It is uncertain if the lactic acidosis was caused by hypotension or the production of cyanide since, in all the dogs studied, changes in lactate, base deficit and oxygen consumption returned to normal spontaneously following discontinuation of SNP. However, the mean changes in plasma lactate followed closely those of the mean plasma HCN, although examination of the individual lactate and plasma HCN values suggests a wide variation in individual response to increased cyanide concentrations. The peak increase in lactate concentrations of 2.38 ± 0.34 mmol litre^{-1} (mean ± SEM) occurred at peak increase in the plasma HCN concentrations of 1.36 ± 0.18 μmol litre^{-1} after 45–60 min infusion with SNP. The development of a significant excess lactate value during the period of infusion confirms that the base deficit and increased lactate concentration may result from some impairment of tissue oxygenation, and indeed a reduction in total body oxygen consumption was associated with these findings. Since the dog appears to metabolize HCN more rapidly than does man, the development of lactic acidosis suggests that SNP 1.5 mg kg^{-1} for infusions of 1 h duration may be approaching the upper safe limit for man. Larger and more significant reversible changes in lactate and oxygen consumption occurred in the dogs receiving equivalent bolus doses of KCN and SNP.

The highly significant correlation between blood lactate and arterial base deficit, which occurred both during and after infusion of SNP ($r = 0.95, P < 0.001$), indicates that the simple and accessible measurement of changes in acid–base balance gives adequate clinical warning of the development of a metabolic acidosis associated with administration of SNP.

Aitken and others (1977) suggest that, in man, increasing lactic acidosis is associated with blood HCN concentrations greater than 20 μmol litre^{-1} (53 μg%). Base deficit was at a maximum 45–180 min after peak cyanide concentrations were reached in four patients who received the highest doses of SNP (0.11–0.26 μmol kg^{-1}; 0.34–0.78 mg kg^{-1}), a finding which these authors attribute to delayed toxic effects of the drug. However, this differs from our findings in the dogs where both lactate and base deficit changed in parallel with the plasma cyanide concentrations. In addition there was no delayed increase in these during the 3 h following infusion. After bolus doses of KCN and SNP the greatest mean lactate and base deficit occurred within 10 and 20 min respectively of the peak blood cyanide concentrations and showed no subsequent increase during the next 3 h. After 15 min infusion with SNP in our dogs a mean increase in lactate of 1.2 mmol litre^{-1} was associated with a *plasma* cyanide concentration of 0.62 μmol litre^{-1}. Thus some lactate production in man may be associated with *blood* cyanide concentrations as low as 20 μmol litre^{-1} (53 μg%; Aitken et al., 1977) or *plasma* concentrations of 0.3 μmol litre^{-1} of HCN. However, this insignificant degree of acidosis would not appear to justify reducing the maximum dose of SNP to as little as 0.5 mg kg^{-1}.

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QUELQUES EFFETS PHYSIOLOGIQUES ET METABOLIQUES DU NITROPRUSSIATE DE SODIUM ET DU CYANURE SUR LE CHIEN

RESUME

On a étudié sur deux groupes de chiens anesthésiés les variations cardiovasculaires et les variations base/acide résultant de l'injection intraveineuse de doses équivalentes de nitroprussiate de sodium (SNP) et de cyanure de potassium (KCN). On a étudié sur un troisième groupe, les variations métaboliques produites par l'infusion intraveineuse de 1,5 mg kg^{-1} de SNP à un débit constant, pendant 1 h. Il s'est produit, par contraste à une baisse de la tension artérielle après le SNP, de l'hypertension et de la tachycardie après l'administration de KCN, avec hyperventilation et augmentation du volume des globules concentrés. Pendant l'infusion de SNP, les augmentations de concentrations de cyanure dans le plasma ont été associées à une augmentation du déficit de la base artérielle, au lactate et à l'excès de lactate dans le plasma ainsi qu'à une diminution de la consommation d'oxygène. La présence d'acidose lactique avec le SNP à raison de 1,5 mg kg^{-1} laisse penser que cette dose pourrait être la dose sûre maximale pour infusion à court terme. Quoiqu'il en soit, toutes ces variations se sont inversées spontanément après que l'on ait cessé le SNP, ce qui indique que le déficit de la base est un moyen de surveillance métabolique approprié pendant l'administration de SNP.

EINIGE PHYSIOLOGISCHE UND METABOLISCHE WIRKUNGEN VON SODIUM NITROPRUSSID UND ZYANID IM HUND

ZUSAMMENFASSUNG

Die kardiovaskulären und Säurebasis betreffenden Wirkungen nach gleichwertigen intravenösen Bolusdosierungen

von Sodium Nitroprussid (SNP) und Potassium Zyanid wurden in zwei Gruppen von anästhesierten Hunden untersucht. In einer dritten Gruppe wurden die metabolischen Veränderungen studiert, die durch eine einstündige, unveränderte, intravenöse Infusion von SNP 1,5 mg kg^{-1} herbeigerufen wurden. Im Gegensatz zu einer Verminderung des arteriellen Drucks nach SNP, traten Hypertonie und Tachykardie nach Verabreichung von KCN auf, mit Hyperventilation und einem angereicherten Erythrozytenvolumen. Während der SNP-Infusion wurden die verstärkten Plasmazyanidkonzentrationen mit einer Vergrosserung des arteriellen Basisdefizits, Plasmalaktats und übermässig viel Laktat, und einer Verringerung im Sauerstoffverbrauch in Verbindung gebracht. Das Auftreten von laktischer Hyperazidität mit SNP 1,5 mg kg^{-1} scheint darauf hin-zu-weisen, dass dies die Maximumdosis für eine ungefährliche Kurzinfusion ist. Wie dem auch sei, alle Änderungen dieser Art kehrten nach einer Unterbrechung der Verabreichung von SNP spontan ins Gegenteil um, damit wurde bewiesen, dass das Basisdefizit während der Verabreichung von SNP ein ausreichender metabolischer Monitor ist.

ALGUNOS EFECTOS FISIOLOGICOS Y METABOLICOS DE NITROPRUSIATO SODICO Y CIANURO EN EL PERRO

SUMARIO

Se han estudiado los cambios cardiovasculares y de base ácida tras la administración de dosis en bolo intravenosas equivalentes de nitroprusiato sódico (SNP) y cianuro potásico (KCN) en dos grupos de perros anestesiados. En un tercer grupo, se estudiaron los cambios metabólicos producidos por la infusión intravenosa de SNP 1,5 mg kg^{-1} a una rapidez constante durante 1 h. En contraste con una disminución en la presión arterial tras la administración de SNP, la administración de KCN produjo hipertensión y taquicardia, con hiperventilación y aumento en el volúmen de células compactas. Durante la infusión de SNP, aumentaron las concentraciones de cianuro en la plasma, lo cual se asoció con un aumento en la deficiencia arterial de base, lactato en la plasma y un exceso de lactato, y una disminución en el consumo de oxígeno. La ocurrencia de acidosis láctica con SNP 1,5 mg kg^{-1} sugiere que ésta posiblemente sea la dosis máxima segura para infusiones de corto plazo. Sin embargo, todos estos cambios fueron invertidos espontáneamente después de suspenderse la administración de SNP indicando que la deficiencia de base sirve adecuadamente como monitor metabólico durante la administración de SNP.

Br. J. Anaesth. (1979), **51**, 89

METABOLISM OF SODIUM NITROPRUSSIDE AND CYANIDE IN THE DOG

C. J. VESEY, P. J. SIMPSON, L. ADAMS AND P. V. COLE

SUMMARY

Blood cyanide (HCN) and thiocyanate (SCN) concentrations were measured at intervals in anaesthetized dogs given bolus doses of sodium nitroprusside (SNP) 1 mg kg^{-1} or potassium cyanide 1.07 mg kg^{-1} and in animals infused with SNP 1.5 mg kg^{-1} for 1 h. Cyanide appeared rapidly in the red cells to give peak concentrations which accounted for more than 90% of the total blood HCN. A delay between the peak plasma and red cell HCN concentrations confirmed that some of the SNP was degraded in the plasma. Comparison of HCN and SCN concentrations with those measured previously in patients receiving an infusion of SNP suggests that the degradation of SNP and detoxication of HCN may be more rapid in the dog. The various pathways of HCN detoxication are discussed in relation to the reduced formation of SCN^- in dogs receiving SNP compared with those receiving KCN.

Since Hermann (1886) noted an intense odour of cyanide (HCN) in the body cavities of animals killed with sodium nitroprusside (SNP) some workers have believed that nitroprusside exerts its hypotensive effect by the production of minor degrees of cyanide poisoning. Johnson (1929) suggested that the hypotensive action was probably a result of the nitrosyl (NO) group of the SNP molecule and excluded cyanide as the cause of both the toxic and pharmacological effects of the drug. Subsequent work showed that cyanide was released from SNP on incubation with tissues (Hill, 1942) and more recently it has been demonstrated in man that infusion of the drug results in increased blood HCN concentrations (Vesey et al., 1974; Davies et al., 1975a; Vesey, Cole and Simpson, 1976; du Cailar, Mathieu-Daude and Deschodt, 1977; Smith et al., 1977). In addition a number of fatalities have been attributed to the release of HCN from infused SNP (Jack, 1974; Merrifield and Blundell, 1974; Davies et al., 1975; Vesey and Cole, 1975). As a consequence, maximum doses of SNP have been suggested (Editorial, 1975; Davies et al., 1975a; Vesey, Cole and Simpson, 1975, 1976; Bennett and Abbott, 1977; Michenfelder, 1977).

The metabolism and physiological effects of the drug have been studied in three groups of dogs with particular reference to cyanide and thiocyanate (SCN) production (Simpson et al., 1977; Simpson, 1978).

One group of dogs received bolus doses of SNP and a second group was given equivalent amounts of cyanide in the form of bolus doses of potassium cyanide (KCN). Plasma HCN and blood lactate concentrations and oxygen consumption were measured in a third group of dogs, infused with SNP 1.5 mg kg^{-1} at a constant rate for 1 h, to obtain an indication of the safety of the recommended maximum total dose for short term infusions.

This paper describes the changes in blood HCN and plasma SCN concentrations; a second paper reports on the associated cardiovascular and acid base changes (Simpson et al., 1979).

METHODS

Mongrel dogs were used in all three experimental groups Details of the mean weights of the dogs and the mean dose of SNP or KCN are shown in table I.

The lethal i.v. bolus dose of SNP for the dog is reported to be about 3.36 μmol kg^{-1} (1 mg kg^{-1}) (Johnson, 1929). This would release the same amount of HCN as would KCN 16.8 μmol kg^{-1} (1.09 mg kg^{-1}). Since this is well below the amount absorbed (40 μmol kg^{-1} or 2.6 mg kg^{-1}) from a lethal oral dose of KCN in the dog (Gettler and Baine, 1938), the animals in group 1 were each given an i.v. bolus dose of SNP 3.36 μmol kg^{-1} in a total volume of 2 ml 0.9% saline and those in group 2 received a mean bolus

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TABLE I. *Experimental groups*

		Weight (kg)		Agent administered	
Group	No. of dogs	Mean	Range	Agent	Dose (μmol kg^{-1} ± SEM)
1	7	23.63	16.3–36.3	bolus SNP	3.36
2	6	21.94	16.8–25.9	bolus KCN	16.46 ± 0.46
3	8	20.65	15.2–33.6	SNP infused for 1 h	5.1 ± 0.23

dose of KCN 16.46 μmol (1.07 mg kg^{-1}) dissolved in 1–2 ml of isotonic saline. The concentrations of the freshly prepared KCN solutions were determined in duplicate before and after administration of an appropriate volume and the mean values used to calculate the exact dose given to each dog.

McDowall and colleagues (1974) found that SNP 5.37 μmol kg^{-1} h^{-1} (1.6 mg kg^{-1} h^{-1}) was the highest dose associated with recovery in baboons, therefore the dogs of group 3 were infused for 1 h with a mean dose of SNP 5.1 μmol kg^{-1} (1.52 mg kg^{-1}). The solution was freshly prepared and administered in 100 ml of isotonic saline from a foil-wrapped bottle by means of an IVAC 201 drip controller. A check was made on the exact volume administered on each occasion by weighing the bottle before and after the infusion.

Anaesthesia was induced with pentobarbitone sodium 25 mg kg^{-1} and maintained with 66% nitrous oxide in oxygen. The animals were kept in a lateral position and the lungs ventilated to Pa_{CO_2} 4.5–5.2 kPa and incremental doses of pentobarbitone (12.5 mg kg^{-1}; 2–4 doses per experiment) were administered as necessary. Pentobarbitone was not given immediately before making measurements, in view of its occasional transient hypotensive effects. Body temperature was monitored with a rectal thermometer and maintained constant by the use of a warming blanket.

A solution of 0.18% saline in 4% dextrose was infused into one foreleg vein to replace blood lost through sampling. The superficial femoral artery of one leg was cannulated for continuous recording of systemic arterial pressure and for sampling arterial blood. The common femoral artery was left intact to prevent the development of ischaemia and localized acidosis in the limb. A catheter was introduced to the femoral vein to ensure that drugs were given centrally. Central venous pressure was monitored via a catheter inserted to the external jugular vein.

A Swan–Ganz catheter was placed in the pulmonary artery of three dogs in each of groups 1 and 2, and in all dogs in group 3. E.c.g., systemic arterial, pulmonary arterial and central venous pressures were recorded continuously using a Devices M19, six-channel recorder.

When a stable state had been reached, simultaneous heparinized samples of mixed venous blood and arterial blood were obtained. Further samples were taken at the following times after the bolus injections (groups 1 and 2): 2, 5, 10, 20, 40, 80, 120, 160 and 240 min. Arterial and venous blood-gas measurements were made with an Instrumentation Laboratories 413 automatic blood-gas analyser. No therapeutic correction was made for the development of metabolic acidoses which occurred in some dogs and which recovered spontaneously in all but one.

In the third group of dogs the same experimental procedure was used. Physiological measurements and blood sampling were undertaken before infusion, at 15, 30, 45 and 60 min during infusion and at 10, 30, 60, 120 and 180 min after termination of the infusion.

The samples of arterial blood, collected in ice-cooled syringes, were centrifuged immediately for 10 min at 2300 rev min^{-1} and 0 °C. The plasma and erythrocytes were separated and analysed for cyanide and thiocyanate by methods described previously (Vesey, Cole and Simpson, 1976).

RESULTS

There was a slower change in both plasma and red cell HCN concentrations and a much smaller plasma HCN concentration following boluses of SNP than following KCN (figs 1, 2). Similarly there was both a slower increase in plasma SCN and a lower peak SCN concentration in group 1 than in those animals receiving a bolus dose of KCN (fig. 3).

The method used for determining plasma SCN (Aldridge, 1945) also measures HCN. Plasma thiocyanate concentrations are much greater than plasma HCN concentrations and it is necessary to dilute the plasma for measurement of SCN. This dilution, in addition to the loss of *plasma* HCN during storage in deep freeze, results in an insignificant

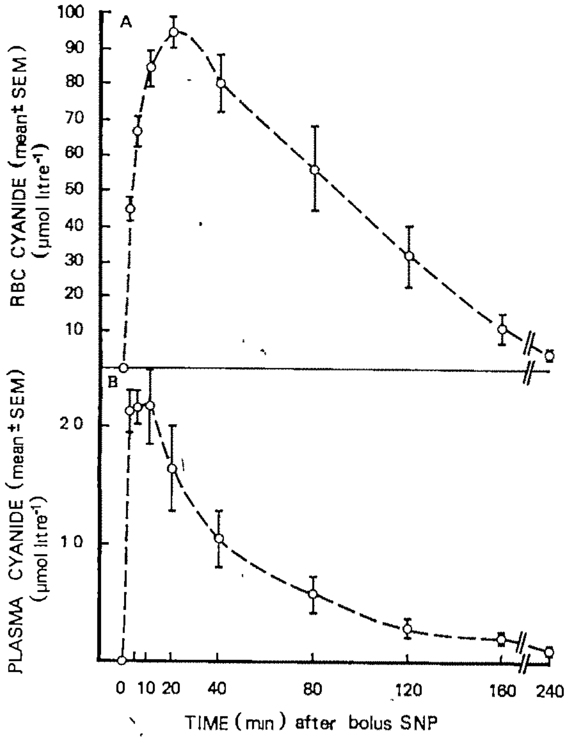

FIG. 1. Red cell (A) and plasma (B) cyanide concentrations in dogs following a bolus dose of SNP 1.0 mg kg⁻¹.

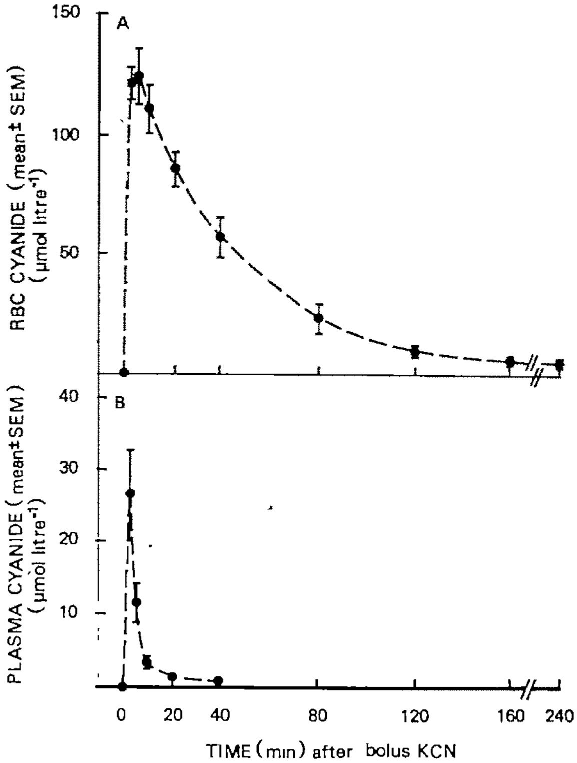

FIG. 2. Red cell (A) and plasma (B) cyanide concentrations in dogs following a bolus dose of KCN 1.07 mg kg⁻¹.

contribution to the SCN result by the cyanide present. However, the dogs of group 2 had very large initial plasma HCN concentrations and the sharp peak at the start of the SCN curve (fig. 3A) is a result of some cyanide remaining after storage at −20 °C. The increase in SCN at this point was obtained by extrapolation and is shown as a dotted line.

The mean plasma and red cell cyanide concentrations and the increase in plasma SCN, measured at intervals during and for 3 h after infusion, are shown in figure 4. The larger amount of SNP given to group 3 dogs results in proportionately greater peak red cell HCN and plasma SCN concentrations than occurred in group 1. As expected, the slow infusion of the SNP dose resulted in a smaller plasma cyanide concentration, although the time scale of the increase in plasma SCN was similar to that of group 1. Both the plasma and red cell HCN concentrations reached a maximum at the end of infusion with a distinct decrease after 10 min.

The plasma HCN concentration curve appears to flatten out 15 min before the end of the infusion. The peak plasma HCN concentration occurred

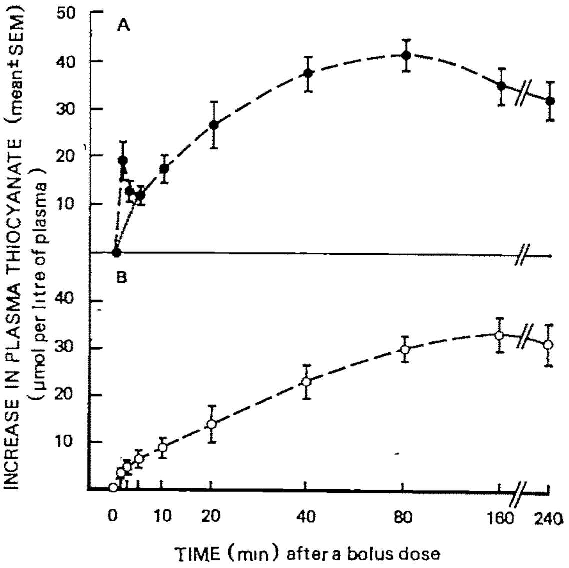

FIG. 3. Increase in plasma thiocyanate concentrations in dogs given bolus doses of (A) KCN 1.07 mg kg⁻¹ and (B) SNP 1.0 mg kg⁻¹.

TABLE II. *Comparison of maximum blood cyanide concentrations* (μ*mol litre*$^{-1}$, *mean* ± *SEM*) *in dogs receiving either potassium cyanide* (*KCN*) *or sodium nitroprusside* (*SNP*)

	Bolus KCN* ($n = 6$)	Bolus SNP* ($n = 7$)	Infused SNP† ($n = 8$)
Time of measured peak plasma HCN (min)	2	5–10	45–60
Time of measured peak RBC HCN (min)	5	20	60 (end of infusion)
Peak plasma HCN	26.4 ± 6.4	2.2 ± 0.3	1.53 ± 0.16
Peak plasma HCN as % of total blood HCN	17.9	3.2	1.52
Peak RBC HCN	124 ± 11.5	95.3 ± 4.6	119.0 ± 8.4
Peak RBC HCN as % of total blood HCN	91.5	98.4	98.7
Plasma HCN at time of peak RBC HCN	11.5 ± 3.1	1.6 ± 0.35	1.54 ± 0.18
RBC HCN at time of peak plasma HCN	121.3 ± 6.7	67.0 ± 4.4	99.0 ± 7.0 (45 min)

* Following the bolus dose blood samples were taken at 2, 5, 10, 20, 40, 60, 120, 160 and 240 min.

† During infusion blood samples were taken at 15-min intervals and after infusion at 10, 30, 60, 120 and 180 min.

before the peak red cell cyanide and a higher proportion of the total blood HCN was present in the red cells following SNP (table II).

One of the dogs in group 2 died 52 min after a bolus dose of KCN 17.85 μmol kg^{-1} (1.16 mg kg^{-1}). The peak plasma HCN was 43.5 μmol litre^{-1} and the peak red cell cyanide was 123.2 μmol litre^{-1} 2 min after the dose. Similar values were measured in one other dog which received KCN 16.77 μmol kg^{-1} (1.09 mg kg^{-1}) and survived for the duration of the experiment.

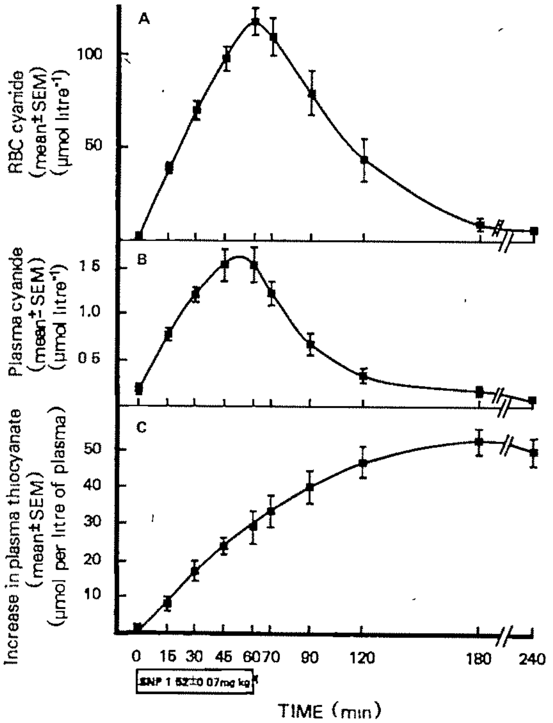

FIG. 4. Red cell cyanide (A), plasma cyanide (B) and thiocyanate (C) during and following infusion with SNP 1.52 mg kg^{-1} for 1 h.

DISCUSSION

The main details of the metabolic pathway of SNP were described by Page and colleagues (1955) and have been reviewed by Davies and others (1975a) and Tinker and Michenfelder (1976). Our understanding of the metabolic processes involved are shown in figure 5. Apart from doubt as to the existence of "thiocyanate oxidase" (Vesey and Wilson, 1978), an enzyme thought to be present in the red cells and responsible for the conversion of SCN to HCN (Goldstein and Reiders, 1953), several uncertainties remain.

As Page and others (1955) suggested, SNP probably reacts with sulphydryl groups (—SH), breaking down to release HCN. In contrast with their data, this reaction occurs to a significant degree in plasma *in vitro*, although it is more rapid in the presence of erythrocytes (Vesey, Cole and Simpson, 1977). Smith and Kruszyna (1974) have proposed that the intact nitroprusside ion ($Fe(CN)_5NO^{2-}$) enters the red cell and reacts with haemoglobin to form one molecule of cyanmethaemoglobin and four molecules of HCN which can then diffuse into the plasma.

The fact that HCN accumulates rapidly in the red cell is illustrated by the results for group 2 (fig. 2, table II). The peak red cell cyanide concentration was five times that of the maximum measured plasma HCN concentrations and occurred within 5 min of injection of a bolus of KCN. In those animals receiving a bolus dose of SNP, the peak red cell HCN

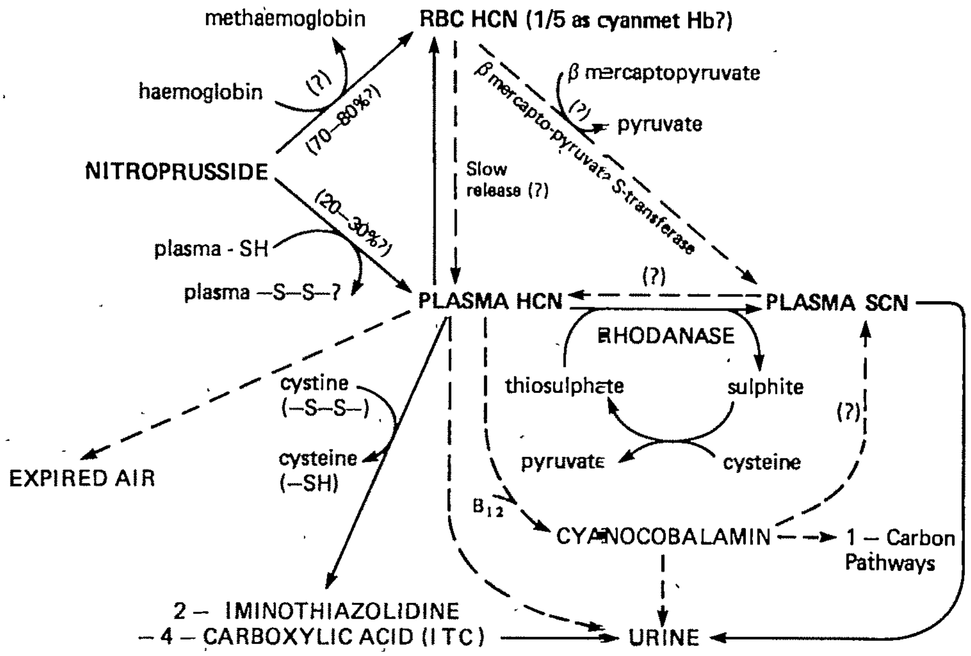

FIG. 5. Pathways of SNP and cyanide metabolism indicating sites for which evidence is inconclusive (?).

similarly occurred after that in the plasma and increased to a value more than 40 times that of the peak plasma HCN (fig. 1, table II). The occurrence of this peak red cell cyanide concentration some 10 min after that in the plasma and the higher proportion of blood cyanide in the red cells after nitroprusside would suggest that breakdown of SNP occurs in both the plasma and the erythrocytes. It is suggested that 20–30% of the breakdown of SNP occurs in the plasma (fig. 5). However, the values for the relative contributions made by the red cells and plasma to the decomposition of SNP in blood are based on *in vitro* studies and it is uncertain if they apply *in vivo* (Vesey, Cole and Simpson, 1977).

In patients 98.4% of the total blood cyanide was found in the red cells at the end of infusion (Vesey, Cole and Simpson, 1976). Similar figures were obtained for dogs given SNP (group 1: 98.4% when r.b.c. HCN reached a peak, and group 3: 98.7% at the end of infusion).

After 60 min infusion of SNP (group 3) the increase in mean plasma and red cell HCN concentration above baseline values were 1.36 ± 0.18 and 118.4 ± 8.3 µmol litre^{-1} (± SEM) respectively. Our previous work (Vesey, Cole and Simpson, 1976) indicates that, following infusion of SNP in man, such values would be expected after total doses of SNP 2.2 and 3.13 µmol kg^{-1} respectively (0.66 and 0.93 mg kg^{-1}), whereas the dogs received an infused dose of SNP 5.1 µmol kg^{-1} (1.52 mg kg^{-1}). This would suggest either that SNP breakdown occurs at a slower rate in the dog or that both SNP decomposition and cyanide metabolism are more rapid in the dog than in man. When the plasma and red cell HCN concentrations 1 h after infusion are compared with those for patients (table III) the mean values in the dogs are smaller, although the mean infused dose of SNP was greater and the period of infusion shorter in the dogs. The decrease in plasma HCN concentration to less than preinfusion values after only 3 h emphasizes the rapid detoxication of HCN in the dog.

Aitken and colleagues (1977) reported that the mean blood cyanide concentrations for 13 patients receiving an infusion of SNP reached a peak within 45 min after the end of infusion. This contrasts with our findings in the dogs, in which the HCN concentration had decreased by 10% 10 min after infusion. These differences may result from the slower metabolism of SNP and HCN in man. However, this may not be the full explanation, since although the highest mean blood cyanide concentration at the end of infusion in our 26 patients (Vesey, Cole and Simpson, 1976) was similar to that measured by Aitken and colleagues (1977), (HCN 25 µmol litre^{-1} blood and

TABLE III. *The increase in plasma and red cell cyanide (μmol litre^{-1}) above pre-dose values in dogs and patients, following infusion with SNP*

	Dogs						Patients†		
	SNP dose	Plasma HCN		RBC HCN		Infusion time (min)	SNP dose	Plasma HCN	RBC HCN
	(μmol kg^{-1})	1 h*	3 h*	1 h*	3 h*		(μmol kg^{-1})	1 h*	1 h*
	4.08	0.21	−0.04	10.24	2.13	95	2.78	1.80	83.87
	6.29	0.22	−0.08	46.41	2.47	168	2.01	0.27	33.77
	5.44	0.65	−0.07	99.13	3.96	95	1.75	0.06	3.40
	5.09	—	−0.26	82.42	7.67	120	2.97	0.85	173.36
	4.71	0.13	—	36.54	1.82	85	2.04	0.04	4.80
	5.35	−0.28	−0.50	14.50	2.08	108	1.68	0.66	39.77
	4.93	0.08	−0.02	35.75	—	141	6.33	1.29	165.00
	5.03	0.02	−0.08	21.59	2.64	80	2.03	0.81	53.92
Mean	5.12	0.15	−0.15	43.32	3.25	111.5	2.70	0.72	69.74
SEM	0.23	0.11	0.07	11.30	0.78	10.68	0.54	0.22	23.56

1-h plasma concentrations significantly different, $t = 2.283$, $0.05 > P > 0.02$; 1-h red cell values not significantly different, $t = 1.011$, $P > 0.1$.

* The HCN concentrations given are for blood samples taken 1 and 3 h after infusion ended. The dogs were all infused for a period of 60 min.

† The data are selected from previously published results (Vesey, Cole and Simpson, 1976) and are for patients who received a total dose of SNP 1.68 μmol kg^{-1} (0.5 mg kg^{-1}) or more during hypotensive anaesthesia for orthopaedic surgery.

24 μmol litre^{-1} respectively), 1 h after the end of infusion the mean concentrations had decreased by 50% in our study compared with a 20% decrease in their patients. The differences may be a result of the dissimilar mean infusion times (86 min and 35.5 min respectively), although the mean doses of SNP administered were also quite different (0.42 mg kg^{-1} compared with 0.22 mg kg^{-1} respectively). A further complicating feature is that, whereas Aitken measured whole blood cyanide in frozen samples, we determined plasma and red cell cyanide separately in freshly taken samples to avoid artefactual formation of HCN from SCN (Vesey and Wilson, 1978), which is probably enhanced by freezing and thawing of *whole blood* (Ballantyne, 1977).

There are at least six known ways by which HCN may be removed from the blood (fig. 5). The major part is converted to thiocyanate (table III). It is considered generally that this is brought about by the mitochondrial enzyme, rhodanase (Sorbo, 1962). The observation that, 3 h after infusion, the plasma HCN concentrations were smaller than the preinfusion values in all the dogs (table III) might suggest that the enzymes involved in detoxication may be induced by exposure to HCN. However, rhodanase activity is not altered following chronic exposure to cyanide in man (Osuntokun, 1972) or in rats (C. Vesey and J. Wilson, unpublished observations).

Comparison of the increase in plasma SCN concentrations in the dogs with those reported previously for patients (Vesey, Cole and Simpson, 1976) suggests also that cyanide detoxication is more rapid in the dog. Thiocyanate concentrations measured in patients 1 h after infusion showed a significant correlation with the total dose of SNP ($r = 0.68$, $P < 0.001$, $y = 1.6 + 6.5x$ (μmol litre^{-1})). A total dose of SNP 5.1 μmol kg^{-1} (1.5 mg kg^{-1}) should produce, therefore, an increase in SCN of 35 μmol litre^{-1} plasma. In the dogs, however, plasma concentrations 1 h after infusion had increased by 45.6 ± 4.3 μmol litre^{-1} (mean ± SEM) in spite of the fact that the dog has a larger thiocyanate space than man (Altmann and Dittmer, 1971).

The increase in *plasma* SCN in the dogs infused with SNP (group 3) was much greater than the increase in *blood* concentration reported by Michenfelder (1977) in a similar study (SCN 50 μmol litre^{-1} *plasma* compared with about 7 μmol litre^{-1} *blood* 2 h after the end of infusion). Thiocyanate concentrations would be expected to be much greater than 7 μmol litre^{-1} since the dogs in Michenfelder's study received 50% more SNP (a total dose of 167.8 μmol SNP (50 mg) compared with a mean of 105.7 ± 12.8 μmol (31.5 mg) in our dogs). In addition, Michenfelder found that there was no difference in blood SCN concentrations between dogs with 10% of their haemoglobin as methaemoglobin and untreated animals following infusion with SNP. In the former group, 60% of HCN was trapped as cyanmethaemoglobin, which would be expected to result in a concentration of SCN smaller than in the untreated dogs. In fact Smith, Mukerji and Seabury (1940) showed that SCN formation was delayed for 2 h in dogs given a dose of sodium nitrite before an injection of sodium cyanide. These discrepancies may be accounted for by the fact that Michenfelder determined *blood* rather than *plasma* SCN. When whole blood is deproteinized with trichloroacetic acid, 80–90% of the SCN is lost; a small amount is converted to HCN (Vesey and Wilson, 1978), whilst the majority is carried down with the precipitated haemoglobin (Goldstein, 1950).

The major part of red cell cyanide is converted to SCN (table IV). This is confirmed by the close correlation between the decrease in mean red cell HCN and the increase in mean plasma SCN in all three groups of dogs (fig. 6). The question remains as to how the red cell cyanide is converted to thiocyanate. The enzyme β-mercaptopyruvate sulphur transferase, which converts HCN to SCN, occurs in red cells (Van den Hamer, Morell and Scheinberg, 1967). However, it seems unlikely that this enzyme contributes significantly to the formation of thiocyanate at this stage, since supply of the substrate β-mercaptopyruvate will be a limiting factor in the erythrocyte. In addition, the red cell seems to be relatively impermeable to SCN (Vesey and Wilson, 1978). It is probable, therefore, that the red cell HCN passes out unchanged into the plasma, and thence into the tissues to be converted to SCN.

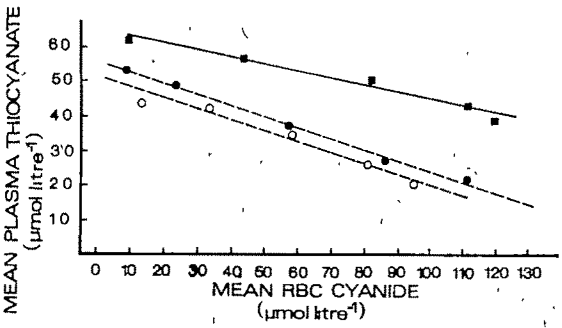

Fig. 6. Increasing mean plasma thiocyanate concentrations plotted against decreasing mean red cell cyanide concentrations in the three groups of dogs. —■— infused dogs (1.52 mg kg^{-1}); $r = 0.99$, $P < 0.001$; - - - ● - - - dogs receiving bolus doses of KCN 1.07 mg kg^{-1}; $r = 0.99$, $P < 0.001$; - - - ○ - - - dogs given a bolus dose of SNP 1 mg kg^{-1}; $r = 0.97$, $P < 0.01$.

The proportion of the cyanide dose converted to SCN was smaller in both groups of dogs receiving SNP than in the group given KCN (table IV). Small amounts of HCN are excreted in expired air (Boxer and Rickards, 1952a; Vesey, Cole and Simpson, 1976) and urine (Boxer and Rickards, 1952b). In addition, small amounts of cyanocobalamin (CNB$_{12}$) are formed (Vesey et al., 1974), some cyanide from which is channelled into 1-carbon pathways whilst the rest of the CNB$_{12}$ is excreted in the urine (Boxer and Rickards, 1952b). It has been postulated also that SCN is formed from CNB$_{12}$ to release hydroxocobalamin (Wokes and Ellis, 1966) which is then recycled, but the evidence is inconclusive. Contrary to some reports (Tinker and Michenfelder, 1976), rhodanase is not dependent on B12 for its action. The conversion of some HCN to cyanate (CNO) and thence to carbon dioxide is a further possibility (Williams, 1959). These additional mechanisms for the removal of HCN would account for only small amounts of cyanide, perhaps some of the 20% not accounted for as SCN in the dogs receiving KCN, but there is no apparent reason why there should be an increased metabolism by these routes following SNP.

Table IV. *The percentage of the cyanide given to each group of dogs which can be accounted for in the thiocyanate space (SCN) and RBC cyanide (HCN)*

Group	Time between dose and peak plasma SCN (min)	% of dose as SCN*	% of dose as RBC HCN*
1—SNP bolus	160	63	2.6
2—KCN bolus	120	82	0.6
3—SNP infusion	120†	64.5	1.8

* Calculated from the concentrations measured at the time of maximum plasma SCN.

† Time from the end of infusion.

The HCN could be trapped as cyanmethaemoglobin following a dose of SNP, as Smith and Kruszyna (1974) suggest. This possibility is not evident from our results since less than 3% of the cyanide dose in all three groups of dogs remained in the red cells when plasma SCN concentrations reached a maximum (table IV).

The metabolically inert compound 2-iminothiazolidine-4-carboxylic acid (ITC) has been detected in the urine of man and of rats exposed to cyanide

(Wood and Cooley, 1956). This compound arises by reaction between HCN and cystine (a disulphide, —S—S—), and cysteine (—SH) is a by-product of the process (fig. 5). Since some SNP is thought to break down by reaction with —SH groups, presumably with the formation of —S—S— groups, it is possible that more HCN will be converted to ITC (possibly encouraged by a cyclic process involving cystine $\underset{\text{HCN}}{\overset{\text{SNP}}{\leftrightarrows}}$ cysteine) than after KCN.

Our results would suggest that at least some of the breakdown of SNP occurs in the plasma and that both the breakdown of SNP and the subsequent detoxication of the cyanide are more rapid in the dog than in patients and thus, although the dog is a useful model for studying the metabolism of SNP and cyanide, caution is required in the extrapolation of these results to patients.

In addition, the major proportion of the blood cyanide arising from SNP is found in the red cells and most of it is converted to SCN; however, a significant proportion of the cyanide from a dose of SNP in dogs is not detoxicated to SCN and this could result from enhanced formation of ITC.

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METABOLISME DU NITROPRUSSIATE DE SODIUM ET DU CYANURE CHEZ LE CHIEN

RESUME

On a mesuré à intervalles les concentrations de cyanures (HCN) et de thiocyanate (SCN) dans le sang de chiens anesthésiés auxquels on avait administré des doses de nitroprussiate de sodium à raison de 1 mg kg^{-1} ou de cyanure de potassium à raison de 1,07 mg kg^{-1}, ainsi que sur des animaux auxquels on avait infusé du SNP pendant 1 h à raison de 1,5 mg kg^{-1}. Le cyanure est apparu rapidement dans les globules rouges pour former des concentrations de pointe qui ont représenté plus de 90% du HCN contenu dans le sang. Le retard constaté entre les concentrations de HCN dans les globules rouges et la pointe dans le plasma confirme qu'une certaine quantité de SNP se dégrade dans le plasma. La comparaison des concentrations de HCN et de SCN avec celles mesurées antérieurement chez les malades recevant une infusion de SNP laisse penser que la dégradation du SNP et la désintoxication du HCN peut être plus rapide chez le chien. Les divers modèles de désintoxication du HCN sont décrits dans cet article en relation avec la formation diminuée de SCN chez les chiens recevant du SNP, par rapport à ceux recevant du KCN.

DER METABOLISMUS VON SODIUM NITROPRUSSID UND ZYANID IM HUND

ZUSAMMENFASSUNG

Konzentrationen von Blutzyanid (HCN) und Thiozyanat (SCN) wurden in zeitlichen Abständen in anästhesierten Hunden gemessen, denen Bolusdosierungen von Sodium Nitroprussid (SNP) 1 mg kg^{-1} gegeben worden waren, oder Potassium Zyanid (KCN) 1,07 mg kg^{-1}, und in Tieren, die eine Stunde lang eine Infusion von SNP 1,5 mg kg^{-1} erhalten hatten. Zyanid erschien sehr schnell in den roten Blutkörperchen und zeigte Höchstkonzentrationen, die für mehr als 90% des ganzen Blutes gültig waren. Ein Zeitunterschied zwischen der HCN-Höchstkonzentration im Plasma und in den roten Blutkörperchen beweist, dass SNP im Plasma etwas entartet wird. Ein Vergleich von HCN- und SCN-Konzentrationen mit den Konzentrationen, die vorher in Patienten gemessen worden waren, die eine Infusion von SNP erhalten hatten, weist darauf hin, dass die Entartung von SNP und die Entgiftung von HCN wahrscheinlich im Hund schneller vor sich geht. Besprochen wurden die verschiedenen Wege der HCN-Entgiftung in Verhältnis zu der verminderten Formation von SCN in Hunden, die SNP erhielten, verglichen mit Hunden, die KCN erhielten.

METABOLISMO DE NITROPRUSIATO SODICO Y CIANURO EN EL PERRO

SUMARIO

Se midieron a intervalos las concentraciones de cianuro (HCN) y tiocianato (SCN) en la sangre de perros anestesiados que recibieron dosis en bolo de nitroprusiato sódico (SNP) 1 mg kg^{-1} o cianuro potásico 1,07 mg kg^{-1} y de animales infundidos con SNP 1,5 mg kg^{-1} durante 1 h. El cianuro apareció rápidamente en las células rojas hasta alcanzar concentraciones máximas que correspondieron a más de un 90% del total de HCN en la sangre. La plasma se demoró más que las células rojas en alcanzar la concentración máxima de HCN, lo cual confirma que parte del SNP se degrada en la plasma. Una comparación entre las concentraciones de HCN y SCN y aquellas medidas anteriormente en pacientes que recibían una infusión de SNP sugiere que la degradación de SNP y la destoxicación de HCN pueden producirse con mayor rapidez en el perro. Se discuten las diversas vías de destoxicación de HCN en relación a la reducida formación de SCN en los perros que recibían SNP a diferencia de aquellos que recibían KCN.

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PRESERVATION OF THE HYPOXIC PULMONARY VASOCONSTRICTOR MECHANISM DURING METHOXYFLURANE ANAESTHESIA IN THE DOG

J. L. B. MARIN, B. CARRUTHERS, M. K. CHAKRABARTI AND M. K. SYKES

SUMMARY

The effect of methoxyflurane on the hypoxic pulmonary vasoconstrictor response in the dog lung was assessed by measuring the redistribution of pulmonary blood flow in response to two levels of unilateral alveolar hypoxia. Methoxyflurane 0.5% had no significant effect on the redistribution of blood flow resulting from the unilateral administration of oxygen 7% or nitrogen and there were no significant differences in Pa_{O_2} between the measurements made during unilateral hypoxia with methoxyflurane and those made during unilateral hypoxia in the control periods.

Previous work utilizing both isolated perfused cat lungs and intact dog preparations has demonstrated that a number of inhalation anaesthetic agents depress the pulmonary vasoconstrictor response to alveolar hypoxia (Sykes et al., 1973, 1975, 1976, 1978; Sykes, Hurtig et al., 1977a, b). On the basis of these experiments it has been postulated that depression of the hypoxic vasoconstrictor mechanism may increase blood flow to underventilated areas of the lung, thus contributing to a decrease in arterial oxygen tension during anaesthesia.

The purpose of the present experiments was to determine whether clinical concentrations of methoxyflurane would depress the hypoxic pulmonary vasoconstrictor mechanism in intact dogs. The activity of this mechanism was assessed by measuring the redistribution of pulmonary blood flow in response to two levels of unilateral alveolar hypoxia, the partition of pulmonary blood flow between the two lungs being recorded continuously throughout the experiment by measuring the radioactivity of the mixed expired gas from each lung whilst xenon-133 solution was infused continuously into the inferior vena cava (Sykes et al., 1977).

METHODS

Seven dogs of various breed, weighing 18–30 kg, were anaesthetized with thiopentone 20–30 mg kg^{-1} i.v. followed by pentobarbitone 60–180 mg i.v. When required, additional small doses of thiopentone were given throughout the experiment.

Preparation

The trachea was intubated with a cuffed endotracheal tube and ventilation of the lungs was controlled with a Cape ventilator at a constant frequency of 15 b.p.m., the tidal volume being adjusted to provide an end-tidal carbon dioxide concentration of 4–5%, as measured by a Hartmann and Braun URAS 4 continuous infra-red analyser.

Cannulae were inserted into the right and left femoral arteries and veins for the measurement of cardiac output by dye dilution, blood sampling, the direct determination of arterial pressure and for the continuous infusion of xenon-133 solution into the inferior vena cava. A Swan-Ganz and a polyethylene catheter were floated into the pulmonary artery for the recording of pulmonary artery and wedge pressures (Fife and Lee, 1965; Swan et al., 1970; Lozman et al., 1974). The pressures were obtained using Consolidated Electrodynamics strain gauges and recorded on a Devices M19 heated stylus recorder, the transducers being calibrated repeatedly against a column of physiological saline.

As soon as the cannulations had been completed a low tracheotomy was performed and a metal double-lumen tracheal divider was inserted (Seed and Sykes, 1972). Each limb of the divider was connected to one of a pair of matched non-rebreathing valves (Sykes, 1969) which were connected by a Y-piece to the Cape ventilator. The cuff on the tracheal divider was inflated and the separation of the ventilation to each lung was checked by pressurizing each lung to +30 cm H_2O whilst the expiratory port of the

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contralateral non-rebreathing valve was connected to a tube dipping under water. Ventilation of all lung lobes was confirmed by measuring Pa_{O_2} when both lungs were ventilated with 100% oxygen and by examining the ventilation of each lobe at autopsy. After the tracheal divider had been positioned correctly the non-rebreathing valves were connected to separate second-stage ventilator circuits which permitted unilateral control of the inspired gas composition (see Sykes et al., 1978, fig. 1). The expired gas from each lung was passed through a fan-assisted mixing unit and thence to a 55-ml glass chamber situated within the collimator of a scintillation detector. Each detector was linked to a counting system and the counts recorded on a two-channel pen recorder running at a paper speed of 1 cm min^{-1}.

Experimental programme

Both lungs were ventilated initially with 100% oxygen and the tidal volume of each side was adjusted to produce an end-tidal concentration of carbon dioxide between 4 and 5%. Ten millilitre of xenon-133 solution (containing 1 mCi ml^{-1}) was diluted with 40 ml of saline and infused into the inferior vena cava at a rate of 4.5–6.0 ml h^{-1}.

When the count rates observed on the recorder had become steady, mean arterial, pulmonary arterial, pulmonary wedge and dynamic airway pressures were recorded and 5-ml arterial and pulmonary arterial blood samples were obtained for duplicate blood-gas analysis using the Radiometer ABL-1 automated blood-gas analyser (Selman and Tait, 1976) and the standard Radiometer electrode system (Sykes et al., 1970). Each set of measurements was completed by duplicate or triplicate determinations of cardiac output using indocyanine green as the indicator, by measurements of the end-tidal carbon dioxide concentrations from each side, and by assessments of body temperature. When the measurements had been completed the ventilating gas to the left lung was changed to oxygen 7% in nitrogen whilst the right lung was ventilated with oxygen 100%. The time course of the diversion of blood flow to the oxygenated lung was observed on the recorder and a second set of measurements was initiated when the diversion had reached its peak. As soon as the measurements had been completed, the ventilating gas to the left lung was changed to nitrogen whilst the right lung was ventilated with oxygen 100%. The time course of the further diversion of blood flow away from the hypoxic lung was observed on the recorder and a third set of measurements was made when the response had reached its peak. Both lungs were ventilated again with oxygen 100% and methoxyflurane was added to the inspired gas on each side from two Blease–Univap vaporizers. The inspired concentrations were checked repeatedly with a Riken refractometer (Hulands and Nunn, 1970). A fourth set of measurements was made after the methoxyflurane had been administered for 30 min and then the response to unilateral alveolar hypoxia with oxygen 7% followed by nitrogen was reassessed, a full set of measurements being made at the peak of each response as described above. Bilateral ventilation with oxygen was then resumed and the methoxyflurane discontinued. Forty-five minutes later a final set of measurements was made on oxygen/oxygen, oxygen/oxygen 7% and oxygen/nitrogen (right lung/left lung).

Calculations

Xenon is a relatively insoluble gas, so that approximately 95% of the injected gas is evolved into the alveoli during its passage through the lungs. Since the ventilation is matched to the blood flow initially and then kept constant throughout the experiment, the mixed expired concentration of xenon-133 is proportional to the distribution of blood flow to each lung.

In the present experiments the hypoxic stimulus was always applied to the left lung so that it proved convenient to express the distribution of blood flow in terms of right-to-left (R/L) ratio of xenon-133 counts. Thus, when the ventilation to both lungs on oxygen was matched correctly the ratio equalled 1, but when unilateral hypoxia to the left lung caused a division of blood flow towards the right lung, the ratio increased.

Statistical analysis of the R/L ratios of blood flow was performed by Wilcoxon's signed rank test, whilst the remainder of the data was subjected to a two-way analysis of variance. Cardiac output was calculated from the area under the indicator dilution curves using the formula derived by Simons and White (1976). All blood-gas tensions were expressed as at body temperature using the correction factors of Kelman and Nunn (1966).

RESULTS

Table I shows the individual measurements of the R/L ratios of blood flow at each stage of the experiment, and the results of the statistical analysis. Mean values are illustrated in figure 1.

The R/L ratios with bilateral oxygen were significantly greater during the administration of methoxy-

TABLE I. *Changes in R/L ratios of xenon-133 counts in response to two levels of unilateral hypoxia before, during and after the administration of methoxyflurane* 0.5% *to seven dogs*

	R/L gases								
	Control 1 (C_1)			Methoxyflurane 0.5%			Control 2 (C_2)		
	A	B	C	D	E	F	G	H	I
Dog No.	O_2/O_2	O_2/O_2 7%	O_2/N_2	O_2/O_2	O_2/O_2 7%	O_2/N_2	O_2/O_2	O_2/O_2 7%	O_2/N_2
1	1.0	1.71	2.62	1.05	1.33	2.43	1.0	2.0	3.0
2	1.0	1.81	2.59	1.0	1.61	2.0	1.0	2.5	2.1
3	1.0	1.35	1.72	1.05	1.70	2.31	1.0	2.12	2.02
4	1.0	1.97	2.02	1.14	2.80	4.0	1.0	3.16	3.63
5	1.04	1.85	2.60	1.13	2.05	3.0	1.09	2.78	3.25
6	1.0	1.54	1.86	1.08	2.22	3.48	1.0	2.95	3.95
7	1.0	1.30	1.95	1.0	2.10	2.75	1.0	1.55	1.87
Mean	1.01	1.65	2.19	1.06	1.97	2.85	1.01	2.44	2.83

Statistical analysis by Wilcoxon's paired rank test:
Changes with O_2/O_2: A *v.* D = $P < 0.01$; D *v.* G = $P < 0.01$; A *v.* G = n.s.
Hypoxic responses: A *v.* B, A *v.* C, D *v.* E, D *v.* F, G *v.* H, G *v.* I = all $P < 0.01$.
Methoxyflurane *v.* controls during hypoxia: B *v.* E = n.s.; E *v.* H = n.s.; C *v.* F = n.s.; F *v.* I = n.s.
$(C_1 - C_2)$ during hypoxia: B *v.* H = $P < 0.01$; C *v.* I = n.s.

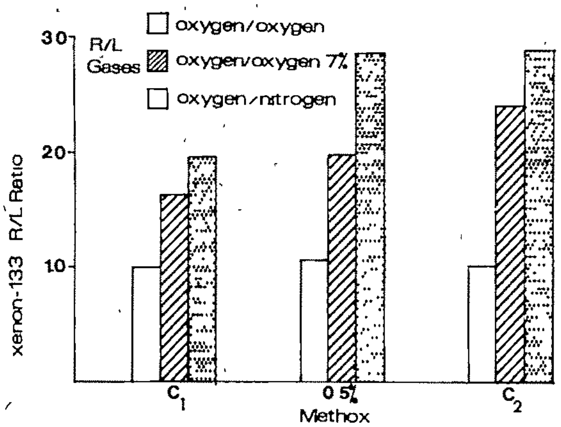

FIG. 1. R/L ratios of blood flow at each stage of the experiment. Means from seven dogs. C_1 and C_2 represent control periods before and after the administration of methoxyflurane 0.5%.

flurane than during the first or second control periods (C_1, C_2) but the magnitude of the differences was small. The diversion of blood flow in response to unilateral nitrogen was greater than the response to oxygen 7% at all stages of the experiment except during C_2 when the response in two of the dogs decreased slightly on changing to oxygen/nitrogen. The responses to hypoxia were generally greater during the second control period than during the first. All the dogs showed a greater response to oxygen/oxygen 7% during C_2 than during C_1 ($P < 0.01$), but two of the dogs showed a smaller response to oxygen/nitrogen during C_2 than during C_1 so that there was no significant difference between the responses for the group as a whole.

Because of these differences between the hypoxic responses in the two control periods, it was difficult to analyse the significance of the responses during methoxyflurane administration. With oxygen/oxygen 7%, two of the dogs showed responses that were smaller than the responses to oxygen/oxygen 7% at C_1 and C_2, one showed a greater response than at C_1 and C_2, whilst the remainder had a response which was greater than C_1 but less than C_2. With oxygen/nitrogen, two of the dogs had responses less than C_1 and C_2, three dogs had responses greater than C_1 or C_2 and two had responses which were less than C_2 but greater than C_1. For the group as a whole there were no significant differences between the responses during methoxyflurane and either of the control periods with either oxygen/oxygen 7%, or oxygen/nitrogen.

The cardiovascular and respiratory measurements are detailed in table II. During ventilation with oxygen/oxygen, mean pulmonary artery pressure ($P_{\overline{PA}}$) and mean pulmonary wedge pressure ($P_{\overline{LA}}$) were significantly greater at C_2 than at C_1, whilst cardiac output ($\dot{Q}$) and mixed venous Po_2 ($P\bar{v}_{O_2}$) were significantly less than at C_1. Cardiac output, $P\bar{v}_{O_2}$ and

TABLE II. *Mean values ± SD of cardiorespiratory measurements for seven dogs in response to two levels of alveolar hypoxia before, during and after methoxyflurane* 0.5%. *Analysis of variance. Comparisons in which* $P < 0.05$ *are indicated by superscript letters in the table*

	R/L gases								
	Control			Methoxyflurane 0.5%			Control		
	A	B	C	D	E	F	G	H	I
	O_2/O_2	O_2/O_2 7%	O_2/N_2	O_2/O_2	O_2/O_2 7%	O_2/N_2	O_2/O_2	O_2/O_2 7%	O_2/N_2
$P_{\overline{AO}}$ (mm Hg)	165.3 ± 21.9	184.3 ± 26.5	185.0 ± 23.2	162.9 ± 22.7	157.1 ± 25.6^{B}	155.0 ± 23.6^{C}	155.0 ± 13.2	164.3 ± 13.9^{G}	163.5 ± 15.9^{C}
$P_{\overline{PA}}$ (mm Hg)	11.1 ± 2.0	13.3 ± 2.2^{A}	13.7 ± 3.1^{A}	11.9 ± 4.0	13.1 ± 4.2^{D}	14.6 ± 5.0^{D}	$15.6 \pm 5.8^{A\ D}$	$18.7 \pm 7.3^{B\ E\ G}$	$19.7 \pm 8.5^{C\ F\ G}$
$P_{\overline{LA}}$ (mm Hg)	4.6 ± 3.1	5.3 ± 3.8	5.3 ± 4.5	6.7 ± 4.9	7.9 ± 4.7^{D}	$8.9 \pm 4.5^{C\ D}$	$10.9 \pm 6.2^{A\ D}$	$12.1 \pm 7.7^{B\ E}$	12.1 ± 9.0^{C}
$\dot{Q}$ (litre min^{-1})	2.0 ± 0.64	1.95 ± 0.3	1.81 ± 0.47	1.22 ± 0.28^{A}	$1.38 \pm 0.28^{B\ D}$	$1.33 \pm 0.27^{C\ D}$	1.14 ± 0.18^{A}	1.30 ± 0.25^{B}	1.37 ± 0.18^{G}
Pa_{O_2} (kPa)	59.4 ± 5.0	22.5 ± 8.0^{A}	17.5 ± 8.5^{A}	62.0 ± 5.1	25.5 ± 9.0^{D}	21.5 ± 10.0^{D}	60.5 ± 4.5	$31.6 \pm 10.0^{B\ E\ G}$	21.5 ± 9.4^{G}
$P\bar{v}_{O_2}$ (kPa)	6.8 ± 0.75	5.9 ± 0.59^{A}	5.5 ± 0.8	5.9 ± 0.82^{A}	$5.1 \pm 0.92^{B\ D}$	$5.0 \pm 1.0^{C\ D}$	5.6 ± 0.97^{A}	4.9 ± 2.1	5.25 ± 1.09
Pa_{CO_2} (kPa)	4.23 ± 0.36	4.32 ± 0.41	4.66 ± 0.68	4.03 ± 0.49	4.25 ± 0.55^{D}	4.41 ± 0.56^{D}	4.13 ± 0.65	4.52 ± 0.40^{G}	$4.64 \pm 0.61^{F\ G}$
$P\bar{v}_{CO_2}$ (kPa)	5.45 ± 0.65	5.4 ± 0.57	5.52 ± 0.59	5.48 ± 0.68	$5.69 \pm 0.64^{B\ D}$	5.33 ± 0.85	5.71 ± 0.69	$5.93 \pm 0.75^{B\ E}$	5.88 ± 0.72^{C}
H^+(nmol litre^{-1})	43	44	44	41^{A}	41	44^{D}	43	45^{E}	$46^{C\ F}$
Hb (g dl^{-1})	14.8 ± 1.9	14.5 ± 1.7	14.6 ± 1.8	14.7 ± 2.0	14.7 ± 1.9	14.4 ± 1.9	14.4 ± 2.2	14.7 ± 2.5	14.7 ± 2.5
BE (mmol litre^{-1})	$-(5.3 \pm 2.1)$	$-(5.0 \pm 2.3)$	$-(4.9 \pm 2.3)$	$-(5.2 \pm 2.3)$	$-(5.0 \pm 1.9)$	$-(5.4 \pm 1.9)$	$-(6.3 \pm 1.6)$	$-(6.2 \pm 1.7)$	$-(6.2 \pm 1.9)$
Airway pressure (cm H_2O)									
R	9.8 ± 1.9	9.9 ± 2.1	9.9 ± 2.0	9.6 ± 1.6	9.7 ± 1.6	9.8 ± 1.7	10.3 ± 1.5	10.5 ± 1.6^{E}	10.3 ± 1.6
L	9.7 ± 2.0	10.0 ± 2.3^{H}	10.7 ± 2.7^{A}	10.3 ± 1.6	10.7 ± 1.7^{D}	11.1 ± 1.6^{D}	11.0 ± 1.7^{A}	11.3 ± 1.4^{G}	11.7 ± 1.4^{G}
PE'_{CO_2}									
R	4.4 ± 0.3	4.7 ± 0.3^{A}	5.0 ± 0.3^{A}	4.1 ± 0.2^{A}	4.7 ± 0.5^{D}	5.0 ± 0.6^{D}	4.2 ± 0.6	4.9 ± 0.8^{G}	5.1 ± 0.8^{G}
L	4.4 ± 0.3	4.0 ± 0.3^{A}	3.5 ± 0.3^{A}	4.1 ± 0.3	$3.6 \pm 0.3^{B\ D}$	3.2 ± 0.5^{D}	4.1 ± 0.6^{A}	3.6 ± 0.8	$3.1 \pm 0.5^{C\ G}$
PVR (mm Hg litre min^{-1})	3.4 ± 1.0^{C}	4.0 ± 1.0	4.6 ± 1.1	4.5 ± 2.1	3.8 ± 1.8^{H}	3.8 ± 1.8	3.8 ± 1.4	4.8 ± 1.9	$5.5 \pm 2.3^{C\ F}$

hydrogen ion concentration (H^+) were significantly smaller during the administration of methoxyflurane than at C_1. Both levels of unilateral hypoxia resulted in increases in mean aortic pressure ($P_{\overline{AO}}$), $P_{\overline{PA}}$ and left airway pressure at all stages of the experiment, whilst end-tidal carbon dioxide ($P_{E'CO_2}$) decreased on the hypoxic side and increased on the non-hypoxic side, thus confirming the shifts of blood flow. Pa_{O_2} values were reduced during unilateral hypoxia, but the blood remained well oxygenated. There was no significant difference between Pa_{O_2} with oxygen/oxygen 7% during methoxyflurane and the values at C_1, but the C_2 values were increased significantly when compared with the other stages of the experiment. This confirmed the marked increase in diversion of flow away from the hypoxic lung at this time (fig. 2). Pa_{O_2} values were less during oxygen/nitrogen than during oxygen/oxygen 7%, but there were no significant differences between the measurements made during the administration of methoxyflurane and C_1 or C_2.

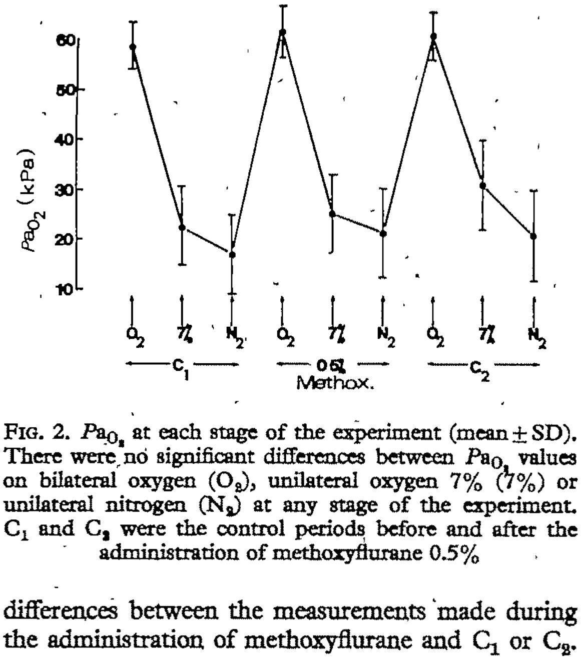

FIG. 2. Pa_{O_2} at each stage of the experiment (mean ± SD). There were no significant differences between Pa_{O_2} values on bilateral oxygen (O_2), unilateral oxygen 7% (7%) or unilateral nitrogen (N_2) at any stage of the experiment. C_1 and C_2 were the control periods before and after the administration of methoxyflurane 0.5%

DISCUSSION

These experiments showed that the administration of methoxyflurane 0.5% to the intact dog produced variable effects on the pulmonary vasoconstrictor response to two levels of unilateral alveolar hypoxia. As a result there was no significant difference between the responses during the administration of methoxyflurane and those obtained during the control periods for the group as a whole. These results differ from observations in isolated perfused cat and rat lungs where the administration of concentrations of methoxyflurane as small as 0.2% produced a significant depression of the responses (Sykes et al., 1976; Bjertnæs, 1977). It is not clear whether the difference was attributable to the type of preparation used, to a failure to achieve a high enough concentration of anaesthetic in the tissues, or to a species difference.

The isolated perfused cat lung preparation was utilized in the earlier experiments with methoxyflurane so that the vasomotor responses to the drug and to alveolar hypoxia could be differentiated from changes in pulmonary vascular resistance secondary to changes in blood flow, vascular or airway pressures or autonomic activity. In this preparation methoxyflurane had a vasodilator action and increasing inspired concentrations produced increasing depression of the pulmonary vasoconstrictor response to alveolar hypoxia. Obviously, such a preparation differs from the intact animal. The systemic and bronchial circulations are not perfused so that autonomic and central nervous system influences are eliminated (Allison, Daly and Waaler, 1961). The lung is perfused with a non-pulsatile flow of oxygenated, heparinized blood and the ligatures round the pulmonary artery and aorta interrupt the lymphatic drainage so that pulmonary oedema occurs after 4–5 h of perfusion. All these factors may make the pulmonary vasculature more sensitive to anaesthetic agents.

When inhalation anaesthetic agents are administered, consideration must be given also to their uptake and distribution. The volume of perfusate in the isolated lung is only 200–300 ml and there are no other tissues in the circuit which can take up the anaesthetic. Therefore equilibrium between inspired, alveolar, blood and tissue concentrations of methoxyflurane must be achieved more rapidly than in the intact dog in which the high solubility of methoxyflurane results in a large difference between inspired and blood and tissue concentrations. Unfortunately, attempts to increase tissue concentrations in the intact dogs by prolonging the administration of methoxyflurane or increasing the inspired concentration failed because of the occurrence of systemic hypotension. However, in two of the dogs in which inspired concentrations of 1% were achieved, no depression of the response was observed.

The disparity between the results which have been obtained with methoxyflurane in the isolated perfused cat lung and the intact dog preparations could be a result of a species difference. A similar difference was observed also with halothane (Sykes et al., 1978). Halothane produced vasodilatation in the isolated cat lung (Sykes et al., 1973) and there was evidence to suggest that halothane may have produced vasodilatation in the dog lung (Benumof and Wahrenbrock, 1975; Mathers, Benumof and Wahrenbrock, 1977) although it appeared to have no effect on pulmonary vascular resistance in the human (Price et al., 1969). Although methoxyflurane was a vasodilator also in the cat (Sykes et al., 1976), it is not known whether it exerts a similar action in other species. In the present studies methoxyflurane produced variable changes in calculated pulmonary vascular resistance. However, these were accompanied by a marked decrease in cardiac output so that it was not possible to draw any valid conclusions as to its effect on pulmonary vascular tone. If a drug produces vasodilatation, it would be expected from the Laplace relationship that a greater increase in wall tension would be required to divert flow in response to hypoxia than when the response was elicited in the normal state. Thus vasodilatation would be expected to diminish the magnitude of the hypoxic response. However, it appears that this mechanism is not very important because the hypoxic vasoconstrictor response is decreased by both vasodilators and vasoconstrictors of the pulmonary circulation (Marin et al., 1978).

There is evidence that both halothane and ether depressed hypoxic vasoconstriction in the human (Bjertnaes et al., 1976), whereas in intact dogs 5% ether depressed the response (Sykes, Hurtig et al., 1977a) and halothane in concentrations up to 2 MAC had no effect (Mathers, Benumof and Wahrenbrock, 1977; Sykes et al., 1978). Because of these species differences it is obviously unwise to extrapolate the results of the present study to man.

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PRESERVATION DU MECANISME PULMONAIRE HYPOXIQUE VASOCONSTRICTEUR PENDANT L'ANESTHESIE D'UN CHIEN A LA METHOXYFLURANE

RESUME

On a évalué l'effet de la méthoxyflurane sur la réaction pulmonaire hypoxique vasoconstrictive sur le poumon d'un chien en mesurant la redistribution du débit sanguin pulmonaire réagissant à deux niveaux d'hypoxie alvéolaire unilatérale. La méthoxyflurane à 0,5% n'a eu aucun effet significatif sur la redistribution du débit sanguin résultant de l'administration unilatérale de 7% d'oxygène ou d'azote et il n'y a eu aucune différence significative dans la Pa_{O_2} entre les mesures prises pendant l'hypoxie unilatérale par la méthoxyflurane et celles prises pendant l'hypoxie unilatérale au cours des périodes témoins.

AUFRECHTHALTUNG DES HYPOXISCHEN, PULMONAREN VASOKONSTRIKTORMECHANISMUS WÄHREND EINER METHOXYFLURANANASTHESIE IM HUND

ZUSAMMENFASSUNG

Festgestellt wurde die Wirkung von Methoxyfluran auf die hypoxische, pulmonare Vasokonstriktorreaktion in der Hundelunge durch Messungen der pulmonaren Blutflussverteilung als Reaktion auf zwei Grade einer einseitigen alveolaren Hypoxie. Als Resultat der einseitigen Verabreichung von 7% Sauerstoff oder Stickstoff hatten 0,5% von Methoxyfluran keinen besonderen Einfluss auf die Verteilung des Blutflusses, und es gab keine bedeutenden Unterschiede im Pa_{O_2} Niveau zwischen den Messungen, die während der einseitigen Hypoxie mit Methoxyfluran gemacht wurden, und denen der einseitigen Hypoxie in den Kontrollzeiten.

PRESERVACION DEL MECANISMO VASOCONSTRICTOR PULMONAR HIPOXICO DURANTE ANESTESIA DE METOXIFLURANO EN EL PERRO

SUMARIO

Se evaluó el efecto ejercido por metoxiflurano sobre la respuesta vasoconstrictora pulmonar hipóxica en el pulmón del perro mediante la medición de la redistribución de la circulación de sangre pulmonar como respuesta a dos niveles de hipoxia alveolar unilateral. Un 0.5% de metoxiflurano no ejerció un efecto significativo sobre la redistribución de la circulación de sangre resultante de la administración unilateral de un 7% de oxígeno o nitrógeno y no se produjeron diferencias significativas en el Pa_{O_2} entre las mediciones tomadas durante hipoxia unilateral con metoxiflurano y aquellas tomadas durante hipoxia unilateral en los períodos de control.

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ATTENUATION OF THE DIURETIC EFFECT OF DOPAMINE BY DROPERIDOL IN MAN AND DOGS

F. Goto, T. Fujita and Y. Fuse

SUMMARY

The effects of dopamine 0.5–6.0 μg kg^{-1} min^{-1} on urine flow and the excretion of sodium and inorganic phosphate were studied in patients and dogs. In both the patients and the animals the diuretic effect of dopamine was augmented by the i.v. administration of droperidol 0.25 mg kg^{-1}. Similarly, the excretion of sodium and inorganic phosphate was increased by droperidol.

Dopamine has, in addition to its alpha- and beta-adrenergic effects, a unique action in that it has been shown to increase renal and mesenteric blood flow (Goldberg, 1972). Indeed, it has been suggested that dopamine acts on a specific receptor in the renal vascular beds (Yeh, McNay and Goldberg, 1969). However, the renal vasodilatation produced by dopamine may be attenuated by haloperidol (Van Rossum, 1966; Yeh, McNay and Goldberg, 1969) whereas that induced by bradykinin and isoprenaline is unaffected.

We have examined the effect of dehydrobenzperidol (droperidol), a derivative of haloperidol, on the activity of dopamine and, in particular, on its effects on the excretion of sodium and inorganic phosphate. Cuche and colleagues (1976) have reported that, in dogs, dopamine caused an increase, not only in the rate of sodium excretion, but also in that of phosphate, and they have shown that this was unrelated to parathyroid hormone activity.

METHODS

Clinical study

Thirty adult patients (ASA class 1 or 2) without evidence of renal impairment were selected. They were undergoing elective surgery (thyroidectomy or mastectomy) and the expected duration of surgery was between 2 and 4 h. All patients were informed of the nature of the experiment in detail and written consent was obtained before the initiation of the study. Atropine 0.5 mg and hydroxyzine hydrochloride 100 mg were administered 1 h before the induction of anaesthesia.

Following the administration of oxygen for 1–2 min, anaesthesia was induced with thiopentone 5 mg per kg of body weight. Endotracheal intubation was performed after the administration of suxamethonium 1 mg kg^{-1}. Halothane 0.5–1.5% in 66% nitrous oxide in oxygen (group 1) and droperidol 0.25 mg kg^{-1}, fentanyl 10–20 μg kg^{-1} and 66% nitrous oxide in oxygen (group 2) were administered randomly. In this latter group, droperidol 0.25 mg kg^{-1} was given before the induction of anaesthesia. Following the induction of anaesthesia the bladder was catheterized with an indwelling balloon catheter and the long saphenous vein was cannulated. In this way urine could be collected readily and its volume measured, and blood could be withdrawn for the determination of the concentrations of the serum electrolytes and of haemoglobin.

In a further group (group 3), anaesthesia was maintained as in group 1, and droperidol 0.25 mg kg^{-1} was administered i.v. during the infusion of dopamine.

Lactated Ringer's solution 500 ml was infused during the 30 min following the induction of anaesthesia. Subsequently, lactated Ringer's solution 500 ml h^{-1} was given. The total mean volume of fluid infused during each study was 1650 ml.

Approximately 1 h after the start of surgery, urine was collected for 30 min (control). Following this, dopamine diluted with saline to 200 μg ml^{-1} was infused at 4–6 μg kg^{-1} min^{-1} for 30 min in groups 1 and 2. Fifteen minutes after the beginning of the dopamine infusion, urine was collected and this was repeated every 15 min thereafter with each collection being terminated by a "washout" with air. A blood sample was obtained at the halfway point and concentrations of the serum electrolytes, the osmotic pressure and the creatinine clearance (glomerular filtration rate) (GFR) were obtained. In group 3, after the infusion of small doses of dopamine (0.5–1.0 μg kg^{-1} min^{-1}) for 30 min, droperidol 0.25 mg kg^{-1} was

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given i.v. and then dopamine was administered for an additional 30 min.

In each patient systolic arterial pressure was measured by sphygmomanometry and care was taken to ensure that there was no alteration in systemic arterial pressure during the infusion of dopamine.

Animal experiments

Twenty-four mongrel dogs of either sex, weighing 6–8 kg, were fasted for 24 h, but allowed free access to water.

The dogs were anaesthetized with pentobarbitone 20 mg kg^{-1} i.v. and following endotracheal intubation the lungs were ventilated with a Harvard Respirator with a mixture of air, oxygen and halothane 0.7–0.9%. The ventilation and inspired gas concentrations were adjusted to maintain Pa_{CO_2} at 3.99–5.32 kPa and Pa_{O_2} at 12.63–17.29 kPa. Oesophageal temperature was maintained at 37 ± 0.5 °C.

Cannulae were inserted into the right femoral vein and into the right femoral artery to permit the infusion of drugs and for blood sampling and arterial pressure recording respectively. A polyethylene cannula was passed into the left ureter via a subcostal incision to enable urine to be collected. The left renal artery was exposed and 0.9% saline 0.25 ml min^{-1} was infused via a 27-gauge curved needle. When required, dopamine was infused into the left renal artery also. Four hour before the start of the dopamine the thyroid and parathyroid glands were removed to prevent alterations in the secretion of parathyroid hormone (PTH) (Fischer, Blum and Binswanger, 1973), since this controls the excretion of phosphate.

In eight dogs following 15 control clearance periods and without altering the volume of saline infused (0.25 ml min^{-1}), dopamine 0.5 μg kg^{-1} min^{-1} was infused into the left renal artery. After allowing 15 min for equilibration, 15-min dopamine clearance periods were obtained. Thereafter, droperidol 0.25 mg kg^{-1} was administered i.v., while the infusion of dopamine was continued for a further 30 min.

In one dog (fig. 4), haloperidol 0.2 mg kg^{-1} was administered during the infusion of dopamine 1.0 μg kg min^{-1} and then 1 h later dopamine 0.5 μg kg^{-1} min^{-1} was infused concurrently with an infusion of haloperidol 0.02 mg kg^{-1} min^{-1}. A 0.9% saline solution was infused 100 ml h^{-1} during every experiment.

The concentrations of creatinine (Steinitz and Turkand, 1940) and phosphate (Fiske and SubbaRow, 1925) in urine and plasma were determined colourimetrically.

Student's *t* test for paired or unpaired data was used for statistical analysis. $P < 0.05$ was considered to represent a statistically significant change.

RESULTS

Clinical study

The changes in systolic arterial pressure, heart rate and renal function associated with the i.v. infusion of dopamine are presented in table I. In groups 1 and 2 urine flow, osmotic clearance and the excretion of sodium and potassium increased markedly with increases in GFR. The increase in urine volume and sodium excretion was more marked in group 1 than in group 2, but the difference between the two groups was not statistically significant.

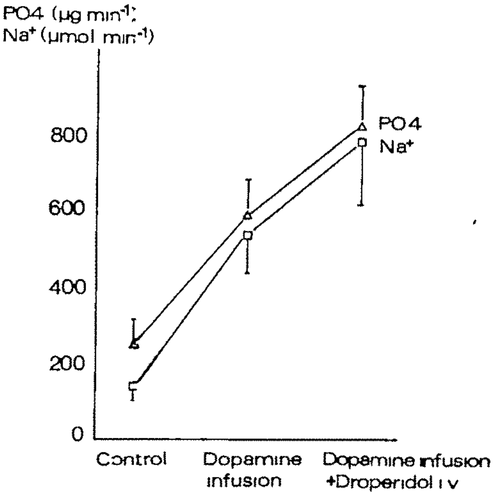

FIG. 1. Effects of dopamine 0.5–1.0 μg kg^{-1} min^{-1} alone and in combination with droperidol 0.25 mg kg^{-1} i.v. on inorganic phosphate and sodium excretion in patients anaesthetized with halothane and nitrous oxide. Sodium and phosphate excretion were increased when droperidol was administered during drip infusion of dopamine ($n = 8$, mean ± SEM).

In group 3 (table I and fig. 1) in which small doses of dopamine were administered, GFR remained unchanged, but urine flow, osmotic clearance and the excretion of sodium and potassium all increased. This increase was augmented to reach values similar to those obtained in group 1 when droperidol had been administered concurrently with the infusion of dopamine. In addition, in group 3, there were significant increases in the excretion of organic phosphate which were of similar magnitude to the osmotic clearance and the sodium excretion.

Arterial pressure and heart rate were unchanged in all groups. Cardiac arrhythmia was noted in one

TABLE I. *Effects of dopamine infusion on surgical patients (mean ± SEM)*

	Urine flow (ml min^{-1})	GFR (ml min^{-1})	Osmotic clearance (ml min^{-1})	Sodium excretion (μmol min^{-1})	Potassium excretion (μmol min^{-1})	Phosphate excretion (μg min^{-1})	Systolic pressure (mm Hg)	Heart rate (beat min^{-1})
Group 1: dopamine 4.0–6.0 μg kg^{-1} min^{-1} ($n = 8$)								
Control	0.69 ± 0.21	63.8 ± 9.2	1.26 ± 0.24	128.6 ± 48.3	47.1 ± 9.8	—	123 ± 4	84 ± 4
Dopamine	5.15 ± 1.25***	89.2 ± 8.8*	7.13 ± 1.78**	710.5 ± 182.1**	90.4 ± 16.9*	—	111 ± 6	84 ± 2
Group 2: dopamine 4.0–6.0 μg kg^{-1} min^{-1} ($n = 8$)								
Control	0.70 ± 0.14	62.0 ± 8.7	2.04 ± 0.33	135.6 ± 42.0	43.6 ± 7.6	—	123 ± 4	80 ± 2
Dopamine	2.97 ± 0.81**	92.9 ± 13.9*	6.27 ± 1.96*	496.0 ± 149.3*	56.3 ± 6.4	—	122 ± 4	89 ± 7
Group 3: dopamine 0.5–1.0 μg kg^{-1} min^{-1} ($n = 8$)								
Control	0.84 ± 0.19	73.2 ± 9.8	1.00 ± 0.28	145.6 ± 39.0	19.2 ± 3.8	254.0 ± 68.0	121 ± 9	88 ± 5
Dopamine	2.48 ± 0.35*	76.7 ± 6.4	4.00 ± 1.00*	545.0 ± 108.1**	51.9 ± 12.5*	593.6 ± 96.3*	105 ± 12	75 ± 10
Dopamine + droperidol 0.25 mg kg^{-1}	4.66 ± 0.77**	80.1 ± 11.5	7.06 ± 1.81**	789.6 ± 178.4**	80.5 ± 21.6*	830.9 ± 107.2**	109 ± 10	90 ± 7

*$P < 0.05$, **$P < 0.02$, ***$P < 0.01$; compared with control period.

TABLE II. *Effect of dopamine on phosphate and sodium excretions in thyroparathyroidectomized dogs ($n = 8$, mean ± SEM)*

	Urine volume (ml min^{-1})	GFR (ml min^{-1})	Plasma PO_4 (μg ml^{-1})	UPO_4V (μg min^{-1})	FE_{PO_4} (%)	Plasma Na^+ (mmol litre^{-1})	UNaV (mmol min^{-1})
Control	0.12 ± 0.02	10.5 ± 1.2	43.0 ± 5.7	10.9 ± 2.0	2.3 ± 0.5	143.0 ± 1.5	37.6 ± 4.3
Dopamine	0.23 ± 0.03*	10.9 ± 1.2	42.4 ± 2.7	18.5 ± 5.5	6.2 ± 1.5*	147.0 ± 1.4	50.6 ± 12.6
Dopamine + droperidol	0.37 ± 0.05**	11.9 ± 1.0	45.0 ± 2.3	47.5 ± 7.0***	10.4 ± 2.0***	146.0 ± 1.2	64.4 ± 12.3*

*$P < 0.05$, **$P < 0.02$, ***$P < 0.01$; UPO_4V, UNaV = phosphate and sodium excretion volumes; FE_{PO_4} = fractional excretion of phosphate. Control 4 h after thyroparathyroidectomy; dopamine 0.5 μg kg^{-1} min^{-1} infusion into the left renal artery; dopamine + droperidol 0.25 mg kg^{-1} administered i.v. during dopamine infusion.

patient in each of groups 1 and 2, but this disappeared immediately after the discontinuation of the infusion of dopamine.

Animal study

The fractional excretion of inorganic phosphate decreased from 16.0% to 2.3% and the good correlation between plasma PO_4 concentration and the fractional excretion ($y = 2.4x+5.25$, $r = 0.74$, $P<0.05$) during normal periods was lost following removal of the thyroid and parathyroid glands (fig. 2).

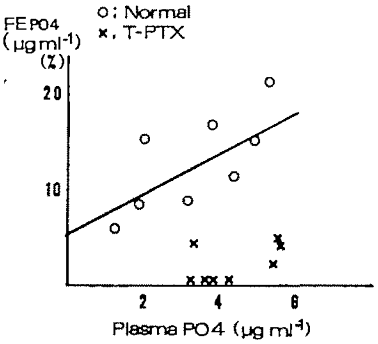

FIG. 2. The correlation between plasma inorganic phosphate concentration and fractional excretion (FE_{PO_4}) during normal periods was lost after thyroparathyroidectomy (T-PTX). $y = 2.47x+5.25$; $r = 0.74$; $P<0.05$.

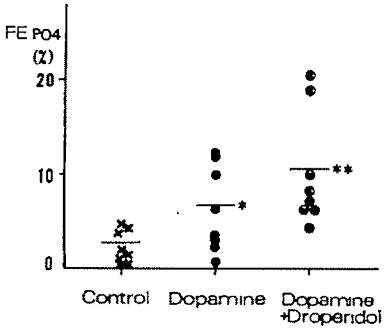

FIG. 3. Effects of dopamine alone and combined with droperidol on inorganic phosphate fractional excretion. I.v. infusion of droperidol 0.25 mg kg^{-1} accelerated fractional excretion of inorganic phosphate (FE_{PO_4}) as a result of dopamine infusion (0.5 μg kg^{-1} min^{-1}). $^{*}P<0.05$, $^{**}P<0.01$, compared with control period.

During the infusion of dopamine alone, the urine volume and the excretion of phosphate increased significantly (table II), but the increases in the excretion of sodium were small and not significant statistically. The i.v. infusion of droperidol 0.25 mg kg^{-1} augmented the increases in urine volume and the excretion of sodium and phosphate (fig. 3).

Dopamine 1.0 μg kg^{-1} min^{-1} increased not only the output of urine and the excretion of sodium and phosphate, but also GFR (fig. 4). However, haloperidol did not affect the diuresis produced by dopamine. Dopamine 0.5 μg kg^{-1} min^{-1} also increased the output of urine and the excretion of sodium during the infusion of haloperidol.

DISCUSSION

The infusion of dopamine 4.0–6.0 μg kg^{-1} min^{-1} to patients produced increases in the volume of urine, GFR, osmotic clearance and the excretion of sodium and phosphate. Similar results have been reported by Goldberg (1972).

When compared with the halothane group (group 1), the diuretic effect was less in group 2, but there was no statistically significant difference between the two groups. In group 3, in which the dose of droperidol was less, a significant diuretic effect was observed also although GFR remained unchanged. The diuretic effect of dopamine was clearly greater when droperidol was administered during the infusion of dopamine. Similar results were observed in the animal studies. Thus it has been shown that the use of droperidol during surgery does not interfere with the diuretic effect of dopamine.

In the central nervous system (Corrodi, Fuxe and Hökfelt, 1967), haloperidol blocks the dopamine receptor in the nigrostriatal tract, and droperidol (Gotoh and Fujita, 1975) exhibits a similar although much weaker action.

Haloperidol (Yeh, McNay and Goldberg, 1969), like other derivatives of butyrophenones, is known to block the effect of dopamine on renal vasodilatation for short periods. However, the present findings indicated that the increases in GFR and the excretion of sodium and phosphate produced by dopamine were not blocked by clinical doses of haloperidol. Moreover, droperidol did not only not block the diuretic action of dopamine, but increased it. Birch and Boyce (1977) reported that droperidol did not attenuate the response of the renal artery to dopamine in man. The results of the present study indicate that the infusion of dopamine will probably be effective in the presence of butyrophenones in man.

Increases in the excretion of sodium induced by doses of dopamine which are of themselves too small to cause significant changes in systemic and renal haemodynamics have been thought to be a result of changes in intrarenal blood distribution as occurs with

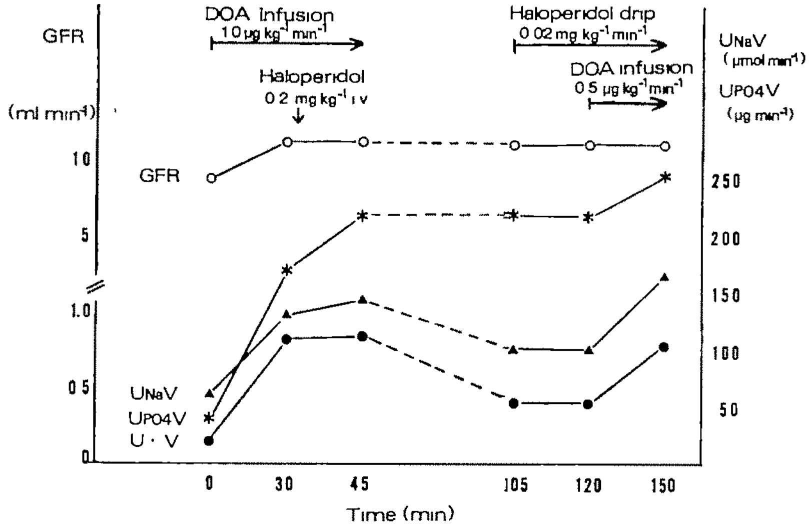

FIG. 4. Effects of dopamine (DOA) alone and combined with haloperidol on GFR, phosphate and sodium excretion volumes in thyroparathyroidectomized dogs.

acetylcholine and papaverine (Meyer, McNay and Goldberg, 1967; Carriere, Friborg and Guay, 1971). However, May and Carter (1970) proved that cholinergic agents, like acetylcholine, inhibit sodium reabsorption in the proximal renal tubule even when administered in doses so small as to induce no change in the intrarenal haemodynamics. Using a micropuncture technique, Seely and Dirks (1967) reported that dopamine decreased sodium reabsorption on the proximal convoluted tubule. According to our studies (unpublished observations), dopamine used in combination with phenoxybenzamine produced a marked increase in action and induced excretion of sodium and phosphate even in small doses (0.002–0.05 µg kg^{-1} min^{-1}, infused into the renal artery) which produced no significant changes in GFR or para-aminohypuric acid excretion in the dog.

Slick and colleagues (1975) and DiBona (1977) reported that the renal sympathetic nerves directly influence renal tubular sodium transport in the absence of alteration in renal haemodynamics. Cuche and others (1976) reported that noradrenaline inhibits the excretion of phosphate. Phosphate is almost completely reabsorbed by proximal renal tubule (Agus et al., 1973; Bank, Aymedijian and Weinstein, 1974). From these findings it is suggested that dopamine acts directly on the proximal renal tubule to inhibit the reabsorption of sodium and phosphate, and the increase in the diuresis produced by dopamine by droperidol is considered to be an effect of the alpha-adrenergic blocking action of the droperidol (Janssen et al., 1963; Muldoon et al., 1977).

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ATTENUATION DE L'EFFET DIURETIQUE DE LA DOPAMINE PAR LE DROPERIDOL CHEZ L'HOMME COMME CHEZ LE CHIEN

RESUME

Les effets de la dopamine, administrée à raison de 0,5–6,0 μg kg^{-1} min^{-1}, sur le débit d'urine et l'excrétion de sodium et de phosphate inorganique ont été étudiés sur des malades et sur des chiens. Chez les malades comme chez les chiens l'effet diurétique de la dopamine a été accru par l'administration intraveineuse de dropéridol à raison de 0,25 mg kg^{-1}. D'une manière similaire, on a augmenté, par le dropéridol, l'excrétion de sodium et de phosphate inorganique.

SCHWÄCHUNG DER DIURETISCHEN WIRKUNG VON DOPAMIN DURCH DROPERIDOL IN MENSCH UND HUND

ZUSAMMENFASSUNG

Die Wirkungen von Dopamin 0,5–6,0 mg kg^{-1} auf den Harnfluss und die Ausscheidung von Sodium und anorganischen Phosphaten wurden in Patienten und Hunden untersucht. In Patienten und Hunden wurde die diuretische Wirkung von Dopamin durch eine intravenose Verabreichung von Droperidol 0,25 mg kg^{-1} verstarkt. Ähnlich wurde auch die Ausscheidung von Sodium und anorganischen Phosphaten durch Droperidol verstärkt.

ATENUACION DEL EFECTO DIURETICO DE DOPAMINA MEDIANTE DROPERIDOL EN EL HOMBRE Y EN PERROS

SUMARIO

Se estudiaron los efectos ejercidos por dopamina 0,5–6,0 μg kg^{-1} sobre la circulación de orina y la excreción de sodio y fosfato inorgánico en pacientes y en perros. Tanto en los pacientes como en los animales el efecto diurético de la dopamina fue aumentado por la administración intravenosa de droperidol 0,25 mg kg^{-1}. De forma semejante, la excresión de sodio y de fosfato inorgánico fue aumentada por droperidol.

Br. J. Anaesth. (1979), **51**, 113

ERGOMETRINE OR OXYTOCIN?

Blood loss and side-effects at spontaneous vertex delivery

D. D. MOIR AND A. B. AMOA

SUMMARY

Blood loss and the frequency of vomiting were assessed at 88 spontaneous vertex deliveries. An i.v. injection of oxytocin 10 u was as effective as ergometrine 0.5 mg in controlling bleeding from the uterus after delivery. The continuous infusion of a dilute solution of oxytocin in the first stage of labour was not followed by an increased blood loss at delivery. Oxytocin infusions were maintained for 1 h after delivery. Vomiting or retching occurred in [illegible]3% of the mothers who received i.v. ergometrine. None of the women who received oxytocin suffered emetic sequelae.

Ergometrine administered i.v. is recognized as an occasional cause of serious postpartum arterial hypertension in normal women and more frequently in patients with pre-eclampsia (Baillie, 1963a, b). The prolonged vasoconstrictor action of ergometrine may be dangerous in a variety of conditions including essential hypertension, congenital and rheumatic heart disease, phaeochromocytoma, thyrotoxicosis and coronary insufficiency.

The cardiovascular side-effects of oxytocin are less recognized. A bolus i.v. injection of synthetic oxytocin causes transient, generalized vasodilatation, sometimes accompanied by hypotension. Arterial hypotension is usually absent or minimal in the lithotomy position (Johnstone, 1972).

I.v. ergometrine is a frequent cause of nausea, vomiting or retching in the conscious patient undergoing operative delivery under extradural analgesia (Milne and Murray Lawson, 1973; Moodie and Moir, 1976).

It was decided to assess the possible influence on third stage haemorrhage of a continuous infusion of oxytocin, given in the first stage of labour and to note the frequency of emetic sequelae in comparison with ergometrine as used routinely.

METHOD

The 88 primigravidae in this study had spontaneous, single, vertex deliveries in the dorsal position. A Crawford wedge was placed under the right buttock for the relief of inferior vena caval occlusion. All infants were at least 36 weeks mature and all were born alive. Analgesia consisted of pethidine i.m. and inhalation of 50% nitrous oxide in oxygen (Entonox). Extradural analgesia was not used. Episiotomy was performed at all deliveries.

The oxytocic drug was chosen by random allocation and was given i.v. at the time of delivery of the anterior shoulder. Ergometrine 0.5 mg was given to 44 patients and 44 received synthetic oxytocin 10 u. A continuous, dilute i.v. infusion of oxytocin was given in the first stage of labour to 52 patients to stimulate or augment uterine action. Oxytocin infusions were controlled by an Ivac drip counter or by a Cardiff pump and continuous recordings were made of the fetal heart rate and uterine contractions. When an oxytocin infusion had been given in the first stage of labour the infusion was continued, at a decreasing rate, for 1 h after delivery.

Blood loss was measured by the haemoglobin extraction–dilution technique, which is acceptably accurate (Roe, Gardiner and Dudley, 1962; Thornton et al., 1963) and particularly suited to obstetric use (Moir and Wallace, 1967; Wallace, 1967). The Perdometer apparatus was used and all blood and blood-stained linen were collected.

The presence or absence of nausea, vomiting or retching after delivery was recorded.

RESULTS

There was no difference in the mean blood loss of the 44 patients who received ergometrine 0.5 mg at delivery and of the 44 patients who received oxytocin 10 u (table I).

The influence of a dilute oxytocin infusion in labour was assessed. Of the 44 patients who received

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ergometrine at delivery, 25 had received an oxytocin infusion in the first stage of labour and there was a mean blood loss of 204 ml at delivery. In the 19 women who received ergometrine at delivery and did not have an oxytocin infusion in labour there was a mean blood loss of 198 ml; this difference is not statistically significant (table II). When the group of 44 patients who received oxytocin at delivery was analysed similarly, there was no significant difference between the average blood loss in those who did and did not receive an oxytocin infusion (table III).

TABLE I. *Blood loss (ml) according to oxytocic drug administered i.v. at* 88 *spontaneous vertex deliveries*

Oxytocic drug	Number of patients	Mean loss (±SD)	Range	No. patients losing more than 500 ml
Ergometrine 0.5 mg	44	201±50	50–950	2
Oxytocin 10 u	44	208±58	40–1100	2

TABLE II. *The effect of an oxytocin infusion in the first stage of labour on blood loss (ml) at spontaneous vertex delivery. All* 44 *patients received ergometrine* 0.5 *mg i.v. at delivery*

Oxytocin infusion	Number of patients	Mean loss (±SD)	Range	No. patients losing more than 500 ml
Yes	25	204.3±47	50–950	1
No	19	198.2±55	70–820	1

TABLE III. *The effect of oxytocin infusion in the first stage of labour on blood loss (ml) at spontaneous vertex delivery. All* 44 *patients received oxytocin* 10 *u i.v. at delivery*

Oxytocin infusion	Number of patients	Mean loss (±SD)	Range	No. patients losing more than 500 ml
Yes	27	208.8±66	40–1100	2
No	17	179.1±50	60–460	None

The frequency of retching or vomiting after delivery in all patients was 13% in patients receiving ergometrine 0.5 mg i.v. at delivery and 0% in those receiving oxytocin 10 u i.v.

DISCUSSION

Ergometrine and other alkaloids of ergot have been of great value in the prevention and treatment of postpartum haemorrhage since their introduction to obstetric practice in the 1930's (Moir and Dale, 1932; Moir, 1934). A pressor effect of i.v. ergometrine was described by Dieckmann, Forman and Phillips in 1950. An emetic action may be observed following i.v. injection in the conscious subject (Moodie and Moir, 1976).

Ergometrine possesses both α and β adrenergic properties, causing vasoconstriction (Johnstone, 1972; Wassef, Lal and Pleuvry, 1974) and an increase in arterial and venous pressure. The frequency of hypertension after i.v. ergometrine was 12% in the study by Hamilton, Higgins and Alsop (1952) and, in the study by Ringrose (1962), 22% of patients exhibited an increase of more than 20 mm Hg in diastolic arterial pressure. Arterial hypertension is more likely to occur in patients with pre-eclampsia (Baillie, 1963a, b). Hypertension occurs 3 min after an i.v. injection of ergometrine and may persist for several hours (Johnstone, 1972). Significant hypertension may follow ergometrine i.m. also, although the onset is less rapid (Cassidy, Moore and Bridenbaugh, 1960).

Ergometrine given i.v. increases the central venous pressure by about 6 cm H_2O when given at delivery and the pressure remains increased for more than 1 h (Vaughan Williams, Johnson and Ledward, 1974). Ergometrine given i.m. increases the central venous pressure by a similar amount, although the pressor response is slower in onset (Greenhalf and Evans, 1970; Vaughan Williams, Johnson and Ledward, 1974). Constriction of the peripheral veins can be demonstrated by plethysmography (Brooke and Robinson, 1970; Johnstone, 1972).

The increase in peripheral vascular resistance which follows the injection of ergometrine may be of serious clinical significance in a minority of patients. In the third stage of labour, in the absence of excessive bleeding, the circulating blood volume is likely to increase with the "autotransfusion" which follows uterine retraction and perhaps the relief of vena caval occlusion. If ergometrine causes vasoconstriction, the hypervolaemia will be relatively greater in the diminished vascular compartment. These changes may precipitate acute pulmonary oedema in patients with heart disease. Arterial constriction is most likely to cause dangerous hypertension and even a cerebrovascular accident, if the patient has pre-eclampsia (Baillie, 1963a, b). Ergometrine has caused cerebral oedema, convulsions and hypertension in a previously normotensive woman (Abouleish, 1976), while its combination with a vasopressor drug, even at an interval of some hours, may cause hypertension and a cerebrovascular accident (Cassidy, Moore and Bridenbaugh, 1960). Retinal detachment has been recorded after ergometrine (Gombes, Howitt and Chem, 1969). Vasoconstriction and hypertension might be hazardous also in the presence of coronary insufficiency, thyrotoxicosis, phaeochromocytoma and anaemia (Johnstone, 1972; Abouleish, 1976). Because the pulmonary and cerebral vessels are less susceptible to adrenergic stimulation than most other vessels, it has been suggested that there may be a special predisposition to pulmonary or cerebral oedema after ergometrine (Johnstone, 1972). The same author has postulated also that the vasoconstrictor action of ergometrine may be diminished by general anaesthesia and that pulmonary oedema might not occur until after recovery from anaesthesia. In these circumstances an erroneous diagnosis of Mendelson's syndrome might be made.

The actions of synthetic oxytocin on the cardiovascular system differ considerably from those of ergometrine. A bolus i.v. injection of oxytocin produces transient dilatation of α and β adrenoceptive vessels and there may be mild hypotension. The vasodilatation occurs within 30 s and lasts 3–5 min (Woodbury et al., 1944; Nakano and Fisher, 1963; Anderson et al., 1965; Hendricks and Brenner, 1970). Synthetic oxytocin is devoid of vasopressin and does not cause hypertension.

In patients anaesthetized for suction termination of pregnancy, the mean arterial pressure decreased by 45% and the mean duration of hypotension was 210 s following oxytocin (Weiss and Peak, 1974). The dilatation of arteries and veins produced by oxytocin was confirmed by Johnstone (1972), who observed that the hypotension which followed a single i.v. injection was a result of posture. In the lithotomy position there was no hypotension in 70% of patients and in the remainder the arterial pressure decreased by less than 15 mm Hg. Continuous infusions of dilute oxytocin in concentrations of less than 20 μu min^{-1} do not cause hypotension (Hendricks and Brenner, 1970). Personal experience with single injections of oxytocin 5 or 10 u at operative and spontaneous delivery suggests that hypotension is not a problem when inferior vena caval occlusion is prevented and blood volume maintained. In only one of 40 patients, who received an i.v. injection of oxytocin 10 u during Caesarean section under extradural analgesia, did the systolic arterial pressure decrease by more than 10 mm Hg. These patients were in the laterial tilt position and had been "pre-loaded" with i.v. fluids (unpublished observations).

When oxytocin 10 u was injected i.v. at delivery the increase in central venous pressure did not exceed 2 cm H_2O, lasting for less than 30 min. These changes are similar to those occurring when no oxytocic drug was given and are substantially less than those produced by ergometrine (Moir, 1970; Vaughan Williams, Johnson and Ledward, 1974).

Because oxytocin reduces peripheral resistance and does not increase arterial or central venous pressures it has important advantages over ergometrine for patients with heart disease or hypertension. The risk of serious hypotension is small if the patient is in the lithotomy position and may be diminished further by preventing vena caval occlusion. If hypotension does occur it should last for not more than 3–5 min. The occurrence of hypotension can be eliminated by giving oxytocin by i.m. injection or by dilute i.v. infusion. In patients with heart disease or hypertension ergometrine should be reserved for atonic postpartum haemorrhage where oxytocin has been ineffective.

In the present study it has been demonstrated that a single i.v. injection of oxytocin 10 u is as effective as an i.v. injection of ergometrine 0.5 mg in preventing third stage bleeding at spontaneous vertex delivery. It is emphasized that where an oxytocin infusion had been used in the first stage of labour, the infusion was maintained at a diminishing rate for 1 h after delivery. In an earlier study oxytocin was as effective as ergometrine in preventing uterine haemorrhage after forceps delivery under extradural analgesia (Moodie and Moir, 1976). There can be no objection to the substitution of oxytocin for ergometrine on the grounds of failure to prevent haemorrhage. The present study failed to demonstrate any significant increase in third stage haemorrhage where an oxytocin infusion was used during labour and where that infusion was maintained for 1 h after delivery.

This study has confirmed also the earlier finding (Moodie and Moir, 1976) that i.v. oxytocin has no emetic action. Vomiting or retching was observed in 13% of the women who received ergometrine i.v. The frequency of an emetic response to ergometrine was much less than the 46% observed following forceps delivery under extradural analgesia (Moodie and Moir, 1976) or the 40% recorded by Milne and Murray Lawson (1973) at Caesarean section under extradural analgesia. The explanation for this difference is uncertain.

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ERGOMETRINE OU OCYTOCINE?

Pertes de sang et effets latéraux lors d'accouchements spontanés lorsque le vertex se présente en premier

RESUME

On a évalué les pertes de sang et la fréquence des vomissements lors de 88 accouchements spontanés avec présentation du vertex en premier. Une injection intraveineuse de dix unités d'ocytocine a été aussi efficace que 0,5 mg d'ergométrine pour maîtriser le saignement de l'utérus après l'accouchement. L'infusion continue d'une solution diluée d'ocytocine au cours des premiers stades de travail n'a pas été suivie d'une perte de sang plus forte lors de l'accouchement. On a maintenu les infusions d'ocytocine pendant 1 h après l'accouchement. Des vomissements et des haut-le cœur ont été constatés dans 13% des cas où l'on avait administré aux mères une injection intraveineuse d'ergométrine. Aucune des femmes auxquelles on avait administré de l'ocytocine n'a souffert de séquelles émétiques.

ERGOMETRIN ODER OXYTOCIN?

Blutverlust und Nebenwirkungen bei spontaner Vorderhauptslagegeburt

ZUSAMMENFASSUNG

Der Blutverlust und die Häufigkeit von Erbrechen wurden in 88 spontanen Vorderhauptslagegeburten bewertet. Um nachgeburtliche Uterusblutungen unter Kontrolle zu bekommen, war eine intravenose Injektion von 10 Einheiten Oxytocin genauso wirksam wie 0,5 mg Ergometrin. Die fortlaufende Infusion einer verdünnten Lösung von Oxytocin wahrend der ersten Geburtsphase hatte keinen verstärkten Blutverlust während der Geburt zu Folge. Oxytocininfusionen wurden noch fur 1 Stunde nach der Geburt weitergegeben. Dreizehn prozent der Mütter, die Ergometrin intravenös erhalten hatten, litten an Brechreiz oder Erbrechen. Keine Frau, die Oxytocin erhaltenhatte, litt an emetischen Folgeerscheinungen.

¿ERGOMETRINA U OXITOCINA?

Pérdida de sangre y efectos colaterales en el parto espontáneo de cabeza

SUMARIO

Se evaluó la pérdida de sangre y la frecuencia de vómitos en 88 partos espontáneos de cabeza. Una inyección intravenosa de 10 unidades de oxitocina surtió el mismo efecto que 0,5 mg de ergometrina en el control de la hemorragia uterina después del parto. La continua infusión de una solución diluída de oxitocina en la primera etapa del parto no fue sucedida por una mayor pérdida de sangre durante el nacimiento. Las infusiones de oxitocina fueron continuadas durante 1 h después del parto. Se produjeron vómitos y vómitos secos en un 13% de las madres que recibieron ergometrina intravenosa. Ninguna de las mujeres que recibieron oxitocina sufrieron secuela emética.

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THE RELATIVE POTENCIES OF THIOPENTONE, KETAMINE, PROPANIDID, ALPHAXALONE AND DIAZEPAM

A statistical study in man

L. STELLA, G. TORRI AND C. L. CASTIGLIONI

SUMMARY

The potency of five i.v. anaesthetics (thiopentone, ketamine, alphaxalone (Althesin), propanidid and diazepam) was studied by determining the dose required to produce unconsciousness in 50% (UD$_{50}$) and 95% (UD$_{95}$) of patients. UD$_{50}$ and UD$_{95}$ were determined using the probit method. The effect of age on the anaesthetic requirement has been studied also. Relative to thiopentone, the potency was alphaxalone 9.22, diazepam 5.24, ketamine 4.37 and propanidid 1.006.

The available data on potency of i.v. anaesthetics have been obtained with different experimental methods, consequently the indices of potency are not comparable (Redish et al., 1958; Egbert, Oech and Echenhoff, 1959; Coleman and Green, 1960; Green and Jolly, 1960; Wyant and Barr, 1960; Dundee, 1963; Thomas, 1967; Clarke et al., 1968).

In the present study the potency of five i.v. induction agents has been investigated by determining the dose required to produce unconsciousness in patients. As age is usually an important factor in determining the dose of an induction agent, potency was investigated in two different age groups.

METHODS

Four hundred and fifty patients (age range 20–50 yr) who were in good general health apart from their presenting surgical complaint were studied. Premedication consisted of atropine 0.5 mg given i.m. 1 h before induction of anaesthesia. The venous return of the arm in which the induction agent was injected was standardized according to the method proposed by Clarke and others (1968). The circulation of the arm was arrested by a sphygmomanometer cuff inflated beyond 200 mm Hg for 3 min. Twenty seconds after releasing the cuff the induction agent was injected into a large antecubital vein. The drug was diluted in a constant volume (10 ml) and injected over 15 s. During injection the patient was asked to count out loud and when this stopped he was asked to respond to a simple command—"open your eyes". If the response was not obtained the patient was stated to be sleeping. If the patient was not sleeping a further dose of the induction drug was injected. As the response (sleeping or not sleeping) in this kind of study is qualitative, a dose–response relationship was obtained by considering the percentage of positive responses (asleep) in groups of patients treated with different doses of the i.v. agents.

Preliminary studies were performed for each anaesthetic on 108 patients to investigate the effect of age on the percentage of positive responses. Two different age groups were selected for each anaesthetic agent: A = age range 20–30 and B = age range 40–50. The patients in each group received the same dose of induction agent to determine if there were any differences in the percentage of positive responses. Statistical analysis (χ^2 test with Yates' correction) showed no relationship between age and the percentage of positive responses. This exercise was repeated for thiopentone, alphaxalone (Althesin), ketamine, propanidid and diazepam, with the same result. Thus, the effect of patient age on dose was not considered further.

In a subsequent phase of the investigation, on 186 patients, we determined for each induction agent the approximate dose (mg kg^{-1}) required to produce unconsciousness in 30, 50 and 80% of patients. It was necessary to do this to utilize the probit method of statistical analysis. Groups of six patients received decreasing doses of drug and this procedure was repeated for each of the five i.v. agents. The three

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doses thus determined were then administered to three groups of patients aged 20–50 yr. This definitive phase of the study was performed on 156 patients. One anaesthetist investigated each of the five induction agents. The percentages of patients found to be asleep following the injection were then converted into probit values and plotted against the logarithmic value of the respective dose. The use of the log/dose scale converts the normal sigmoid dose–response curve to a straight line. By means of probit analyses the values of UD_{50} (unconsciousness dose 50) and UD_{95} (unconsciousness dose 95) were determined for the five induction agents under investigation. The angular coefficient (AC), the r^2 coefficient and the linearity of each log dose/probit relationship were estimated.

RESULTS

In the two age groups studied initially, there was no statistical difference in responses of the groups to the same dose of induction agent (table I). The doses required to produce unconsciousness in about 30, 50 and 80% of patients (table II) were utilized for probit analysis to calculate the UD_{50} and UD_{95} values. The calculation used to estimate the UD_{50}, UD_{95}, the angular coefficient of the line log dose/probit, the r^2 coefficient and χ^2 for linearity is shown in table III. The value $1/UD_{95}$ has been considered as an index of potency. The potency of thiopentone was assumed to be unity.

TABLE I. *2×2 contingency tables for thiopentone, diazepam, propanidid, alphaxalone and ketamine. Age and percentage of positive responses are independent*

		Age (yr)		
		20–30	40–50	χ^2
Thiopentone	sleeping	5	3	0.21 (n.s.)
2.1 mg kg^{-1}	not sleeping	5	7	
Diazepam	sleeping	1	4	0.82 (n.s.)
0.35 mg kg^{-1}	not sleeping	9	7	
Propanidid	sleeping	6	8	0.13 (n.s.)
1.8 mg kg^{-1}	not sleeping	4	5	
Alphaxalone	sleeping	7	5	0.04 (n.s.)
0.272 mg kg^{-1}	not sleeping	4	5	
Ketamine	sleeping	3	3	0.12 (n.s.)
0.12 mg kg^{-1}	not sleeping	8	9	

These values are shown in table IV, which also indicates the AC value of the log dose/probit lines. The potency of propanidid is very similar to that of thiopentone (relative potency = 1.006); ketamine and diazepam had relative potencies of 4.37 and 5.24 respectively. Alphaxalone (Althesin) had the highest potency (relative potency = 9.22). The angular coefficient of the log dose/probit represents the sensitivity of the central nervous system to changes in injected dose. The coefficients of propanidid, ketamine and diazepam were similar and less than for thiopentone. In contrast, c.n.s. sensitivity for alphaxalone (Althesin) was greater than that for thiopentone. Potency and the angular coefficient did not change in the same way. In the case of ketamine high potency was combined with a low angular coefficient value, whereas alphaxalone (Althesin) exhibited both high potency and angular coefficient values.

TABLE II. *Dose (mg kg^{-1}) producing unconsciousness in about 30, 50 and 80% of patients obtained in the preliminary phase of study and used in the definitive phase; number of patients, number of positive responses and percentages obtained in the definitive experiment*

	Dose (mg kg^{-1})	No. of patients	No. of positive responses	%
Thiopentone	2	10	2	20
	2.2	10	5	50
	2.4	10	8	80
Diazepam	0.3	10	2	20
	0.33	10	4	40
	0.4	10	7	70
Propanidid	1.5	10	3	30
	1.75	11	5	45
	2	11	8	73
Ketamine	0.3	10	1	10
	0.4	12	6	50
	0.5	10	8	80
Alphaxalone	0.27	10	3	30
	0.2725	10	5	50
	0.275	12	7	59

DISCUSSION

Anaesthetic potency may be expressed in various terms; (1) as the amount of drug required to produce a desired degree of cerebral depression (Egbert, Oech and Echenhoff, 1959), (2) as the minimum amount to produce sleep (Clarke et al., 1968) and (3) as the time of onset of sleep or as the dose required to produce anaesthesia in a given time (Carson, Dundee and Clarke, 1975). Obviously it would be more correct to relate a defined arterial or cerebral concentration to a level of anaesthesia. However, this is obviously inapplicable to i.v. anaesthetics, because of individual variation in pharmacokinetics.

TABLE III. *Probit analysis values: X = log dose values; Y_p = provisional probit values; Y_w = working probit; W = weight. The X values of the experimental doses less than zero were obtained by subtracting the log dose value from one. The values indicated as a and b are respectively the intercept and the slope of the log dose/probit line. Goodness of fit is tested by χ^2*

X	%	Y_p	Y_w	W	$\overline{X}$	$\overline{Y}_w$	Sx^2	Sy_w^2	SxY_w	a	b	χ^2	r^2
Diazepam													
0.48	20	4.21	4.16	0.502	0.53	4.83	0.041	5.05	0.452	−1.06	11.01	0.0691	0.987
0.52	40	4.66	4.75	0.616	UD_{50} = 0.550 (log dose) = 0.354 (mg kg^{-1})								
0.60	70	5.54	5.52	0.580	UD_{95} = 0.699 (log dose) = 0.500 (mg kg^{-1})								
Propanidid													
0.18	30	4.42	4.48	0.557	0.24	5.0	0.04	3.51	0.4	2.71	9.47	0.134	0.97
0.24	45	4.98	4.87	0.636	UD_{50} = 0.242 (log dose) = 1.747 (mg kg^{-1})								
0.30	73	5.55	5.61	0.557	UD_{95} = 0.415 (log dose) = 2.602 (mg kg^{-1})								
Ketamine													
0.48	10	3.75	3.72	0.370	0.602	4.951	0.10	9.348	0.965	−0.837	9.62	0.28	0.995
0.60	50	4.91	5.0	0.634	UD_{50} = 0.607 (log dose) = 0.404 (mg kg^{-1})								
0.70	80	5.88	5.84	0.471	UD_{95} = 0.777 (log dose) = 0.599 (mg kg^{-1})								
Thiopentone													
0.3	20	4.16	4.16	0.502	0.339	4.984	0.016	6.861	0.327	−2.14	21.0	0	1.0
0.34	50	5.0	5.0	0.636	UD_{50} = 0.340 (log dose) = 2.188 (mg kg^{-1})								
0.38	80	5.84	5.84	0.471	UD_{95} = 0.418 (log dose) = 2.619 (mg kg^{-1})								
Alphaxalone													
0.431	30	4.52	4.48	0.580	0.435	4.933	0.00021	1.871	0.019	−35.26	92.317	0.09	0.952
0.435	50	4.9	5.0	0.634	UD_{50} = 0.436 (log dose) = 0.273 (mg kg^{-1})								
0.439	59	5.28	5.23	0.616	UD_{95} = 0.454 (log dose) = 0.284 (mg kg^{-1})								

TABLE IV. *Relative potencies (RP) and angular coefficient (AC) of the five i.v. anaesthetics. The potency of thiopentone was considered as unity*

	RP	AC
Thiopentone	1	2.1
Ketamine	4.37	9.62
Propanidid	1.006	9.47
Alphaxalone	9.22	92.32
Diazepam	5.24	11.01

The response of the patient considered in the present study is simple to elicit and is reliable.

The values of UD_{50} and UD_{95} considered in the present study have two different meanings; UD_{50} must be considered as a pharmacological index whilst UD_{95} can be regarded as a clinical index because it approaches the first stage of anaesthesia. The observed values of UD_{50} and UD_{95} for the five anaesthetics under study are quite different. The smaller the value of UD_{50} and UD_{95} the greater is the anaesthetic

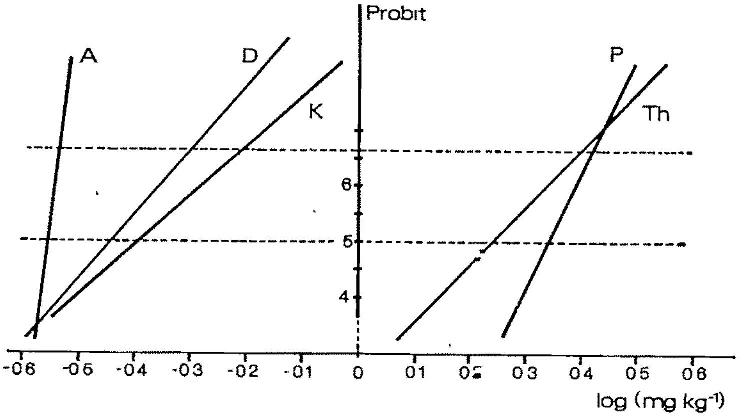

FIG. 1. Log dose/probit lines; A = alphaxalone, D = diazepam, K = ketamine, P = propanidid and Th = thiopentone. Logarithms of values less than zero are negative. The upper dashed line represents UD_{95}, the lower one UD_{50}.

potency. Of the five agents studied alphaxalone (Althesin) had a very high potency while that of thiopentone was least. The potency ratio of alphaxalone (Althesin) to thiopentone (relative potency) observed in the present study is 9.22. This figure is similar to the value observed by Tammisto and others (1973) in a previous similar study. UD$_{50}$/UD$_{95}$ is not the same for the five agents because the log dose/probit relations are not parallel. This means that the relative potency of anaesthetic agents may not necessarily be the same when different end-points are considered. For this reason the clinical implications of the present study should be accepted with reservation, because the anaesthetic potency has been determined at a level which may not correspond to a clinical level of surgical anaesthesia.

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EFFICACITES RELATIVES DU THIOPENTONE DE LA KETAMINE, DU PROPANIDID, DE L'ALPHAXALONE ET DU DIAZEPAM

Etude statistique sur l'homme

RESUME

On a étudié l'efficacité de cinq agents anesthésiants (le thiopentone, la kétamine, l'alphaxalone (Althésine), le propanidid et le diazépam), administrés par voie intraveineuse en déterminant la dose requise pour produire une perte de conscience sur 50% (UD$_{50}$) et sur 95% (UD$_{95}$) des malades. UD$_{50}$ et UD$_{95}$ ont été déterminés par la méthode probit. On a également étudié l'effet de l'âge sur les besoins en agent anesthésiant. Par rapport au thiopentone, leur efficacité a été la suivante: alphaxalone 9,22, diazépam 5,24, kétamine 4,37 et propanidid 1,006.

DIE RELATIVEN STÄRKEN VON THIOPENTON, KETAMIN, PROPANIDID, ALPHAXALON, UND DIAZEPAM

Eine statistische Untersuchung im Menschen

ZUSAMMENFASSUNG

Untersucht wurden die Stärken von fünf intravenösen Anästhetika: Thiopenton, Ketamin, Alphaxalon (Althesin), Propanidid und Diazepam, indem man die Dosierung feststellte, die benötigt wurde, um Bewusstlosigkeit in 50% (UD$_{50}$) und 95% (UD$_{95}$) von Patienten herbeizuführen. UD$_{50}$ und UD$_{95}$ wurden durch die "probit" Methode festgestellt. Auch die Beeinflussung des Menschenalter auf die anästhesierende Dosierung wurde festgestellt. Relativ zu Thiopenton waren die Stärken: Alphaxalon 9,22, Diazepam 5,24, Ketamin 4,37 und Propanidid 1,006.

LAS POTENCIAS RELATIVAS DE TIOPENTONA, KETAMINA, PROPANIDIDA, ALFAXALONA Y DIAZEPAM

Un estudio estadístico en el hombre

SUMARIO

Se estudió la potencia de cinco anestesias intravenosas (tiopentona, ketamina, alfaxalona (Altesina), propanidida y diazepam) mediante la determinación de las dosis necesarias para producir inconciencia en 50% (UD$_{50}$) y 95% (UD$_{95}$) de los pacientes. El UD$_{50}$ y el UD$_{95}$ se determinaron mediante el método "probit". También se ha estudiado el efecto ejercido por la edad sobre el requerimiento de anestesia. En relación con la tiopentona, la potencia de alfaxalona fue de 9,22, diazepam 5,24, ketamina 4,37 y propanidida 1,006.

Br. J. Anaesth. (1979), **51**, 123

INFLUENCE OF AIRWAY RESISTANCE AND VENTILATORY PATTERN ON Pa_{CO_2} DURING ENFLURANE ANAESTHESIA

W. M. Wahba

SUMMARY

Tidal volume, respiratory frequency and Pa_{CO_2} were measured in 21 healthy, premedicated adults during anaesthesia with enflurane and 60 or 66% nitrous oxide in oxygen. The increase in Pa_{CO_2} correlated with the value of FEV_1/VC determined before anaesthesia. Pa_{CO_2} during anaesthesia correlated with an index of airway resistance (FEV_1/height) and was influenced by the pattern of breathing. These correlations are similar to those reported for halothane.

Pa_{CO_2} during halothane anaesthesia with spontaneous ventilation is related to the severity of airway obstruction before operation and to tidal volume during anaesthesia (Pietak et al., 1975). There was a significant correlation between Pa_{CO_2} and the ratio of tidal volume to surface area (V_T/SA) and forced expiratory volume standardized for height (FEV_1/ht). The purpose of the present study was to determine if similar relationships exist for enflurane. Apart from the brief comments by Lebowitz, Blitt and Dillon (1970), no published data could be found on the pattern of breathing during enflurane anaesthesia when premedication, induction and maintenance are standardized. Therefore a pattern was sought from the present data.

METHODS

The study was performed on 21 clinically healthy adults undergoing elective operations on the extremities. The study was approved by the Hospital Research and Ethics Committee. The general and lung function data are shown in table I.

On the day before operation, FEV_1 and vital capacity (VC) were determined from three measurements with the patients seated upright. Blood was sampled from a radial artery by direct puncture while the subject was supine and breathing a mixture of 33% oxygen in nitrogen from a venturi-type mask. The blood was withdrawn anaerobically into heparinized syringes, which were packed in ice. The sample was analysed within 10 min for gas tensions and pH by standard electrodes calibrated with nominal 0, 5 and 10% mixtures of carbon dioxide (Corning 165). No corrections were made for time, thus introducing a possible error of 0.01–0.07 kPa for Pa_{CO_2} (Kelman and Nunn, 1966).

Premedication consisted of anileridine and promethazine by i.m. injection 1 h before operation. The doses (based on body weight) ranged from 12.5 to 37.5 mg of the former, and 12.5 to 25 mg of the latter. Anaesthesia was induced with thiopentone 2–3 mg kg^{-1} i.v. followed by suxamethonium 1 mg kg^{-1} to facilitate orotracheal intubation. Anaesthesia was maintained with enflurane in either 33% or 40% oxygen in nitrous oxide at a fresh gas flow rate of 4.5 or 6.0 litre min^{-1}. The breathing system was a semi-closed circle with carbon dioxide absorption and a low-resistance, uni-directional valve. Following endotracheal intubation, the lungs were ventilated manually until spontaneous breathing was deemed adequate. The vaporizer (Cyprane) was adjusted to deliver a concentration of enflurane which abolished the response to surgical stimulation. In 19 patients concentration in the fresh gas was between 1.5 and 3%; in two the concentration was greater than 3%. (These two patients did not exhibit distinct differences in breathing pattern or P_{CO_2} compared with the others). Twenty to thirty minutes after the start of the operation and when a steady tidal volume and frequency had been present for 5 min, arterial blood was sampled as described above. Expired minute volume ($\dot{V}_E$) was measured with a Wright respirometer connected to the uni-directional valve without disconnecting the patient from the breathing circuit. The data were analysed using Student's *t* test and by least squares regression.

RESULTS

Pa_{CO_2} and ventilation values during anaesthesia are given in table II. Mean V_T during enflurane

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TABLE I. *Biometric data and pulmonary function tests*

	Age (yr)	Weight (kg)	Height (cm)	Surface area (m^2)	FEV/VC (%)	Pa_{CO_2} (kPa)	Pa_{O_2} (kPa) ($FI_{O_2} = 0.33$)
Mean	51.7	67.2	168.5	1.73	85	4.69	17.45
SEM	3.6	2.9	1.8	0.04	2	0.73	0.73

TABLE II. *Values for expired gas volumes, frequency and* Pa_{CO_2} *during anaesthesia*

	V_T (ml)	f (b.p.m.)	$\dot{V}_E$ (litre min^{-1})	V_T/SA (ml m^{-2})	Pa_{CO_2} (kPa)
Mean	332	16.1	5.51	190	7.56
SEM	28	0.4	1.9	60	0.37

anaesthesia was 332 ± 28 ml (SEM) at a mean frequency of 16.1 ± 0.4 b.p.m. The values are different from those noted during halothane anaesthesia. Hickey and colleagues (1973) reported a mean V_T of 245 ± 18 ml and $\dot{V}_E$ 7.0 ± 0.5 litre min^{-1}. In their study mean Pa_{CO_2} was 6.98 ± 0.29 kPa—less than the mean Pa_{CO_2} (7.56 ± 0.37 kPa) noted for enflurane in spite of a greater V_T.

Pa_{CO_2} was increased during anaesthesia in all the patients in the present study, from a mean value on the day before operation of 4.69 ± 0.73 kPa to 7.56 ± 0.37 kPa ($P < 0.001$). This increase was related inversely to $FEV_1/FVC\%$:

$$10.08 - 0.08 FEV_1/FVC \quad (r = 0.6, P < 0.01)$$

During anaesthesia mean pH was 7.21 ± 0.01 units, denoting respiratory acidaemia since the plasma bicarbonate concentration did not change significantly.

Pa_{CO_2} during anaesthesia correlated with minute volume and with FEV_1:

(1) $Pa_{CO_2} = 9.63 - 0.8 \dot{V}_E/SA$ (litre m^{-2}) ($r = 0.79$, $P < 0.001$) (fig. 1);

(2) $Pa_{CO_2} = 9.17 - 1.20 FEV_1/ht$ (litre m^{-1}) ($r = 0.65$, $P < 0.001$) (fig. 2)

(where SA = surface area).

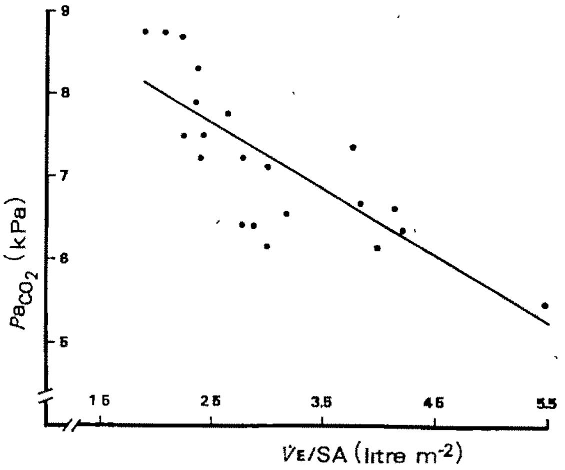

FIG. 1. The influence of $\dot{V}_E$/SA on Pa_{CO_2} during enflurane anaesthesia.

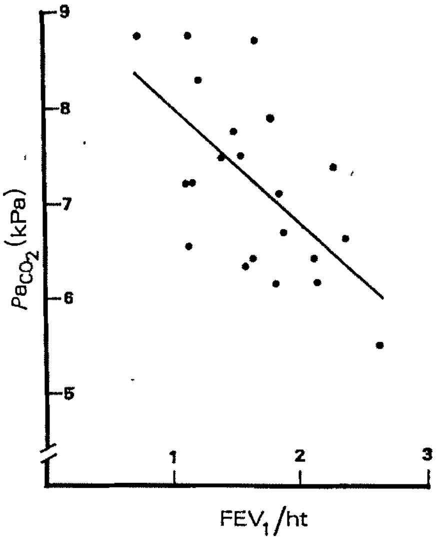

FIG. 2. The relationship between intraoperative Pa_{CO_2} and FEV_1/ht.

DISCUSSION

The anaesthetic technique used in the present study may be criticized because narcotic premedication was given and because each patient did not receive the same concentration of the inhalation agent. Under such conditions, it is impossible to separate the effects of premedication and different concentrations of the agent. Nevertheless, we preferred to give these patients the anaesthetic that they would have received normally for their operation.

When carbon dioxide production and physiological deadspace are constant, hypercarbia is a result of shallow or slow breathing, or both. The average tidal volume noted during enflurane anaesthesia is definitely larger than that reported by Hickey and his co-workers (1973) during halothane anaesthesia. However, such a relatively large tidal volume was insufficient to maintain normocarbia because of the low frequency. An inverse relationship was found between tidal volume and Pa_{CO_2} similar to that reported for halothane by Pietak and others (1975). The data from the present study are presented in the form of $\dot{V}_E/SA$ because this form takes frequency into account (fig. 1).

Forced expiratory volume/vital capacity is a good index of airways resistance because it takes into account individual variations in absolute lung volume. The increase in Pa_{CO_2} which occurred during anaesthesia could be correlated significantly with this index while the absolute value of Pa_{CO_2} had a significant inverse relationship with FEV_1/ht (fig. 2). This relationship has two clinical implications. Awake subjects with high airway resistance can overcome impedance to ventilation by an increase in chemical drive. This response is lessened with anaesthesia, appropriate compensation cannot occur, and minute ventilation tends to decrease. Indeed, we found a direct relationship between $\dot{V}_E/SA$ and FEV_1/ht:

$$\dot{V}_E/SA = 0.62 + 1.47 FEV_1/ht$$

($r = 0.76$, $P < 0.001$) (fig. 3).

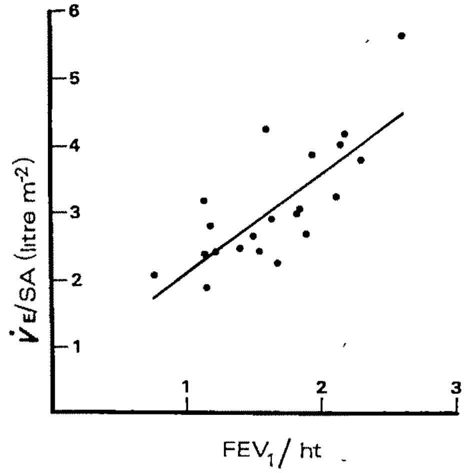

FIG. 3. $\dot{V}_E/SA$ as a function of FEV_1/ht.

The other important consideration concerns the expected reduction in functional residual capacity (FRC) during anaesthesia. Resting lung volumes (FRC) decrease during anaesthesia and the reduction is a function of body build and FEV_1/FVC (Hickey et al., 1973). Airway resistance increases in a hyperbolic fashion as lung volume decreases (Nunn, 1977). Thus, subjects with an initial high airway resistance (low FEV_1) have greater reductions in FRC and greater increases in airways resistance, and this would compound the problem of the effect of increased impedance on minute ventilation mentioned above. Consequently, elimination of carbon dioxide would be hampered severely. It is conceivable that reducing airways resistance with a bronchodilator may lower carbon dioxide tensions secondary to decreasing airway resistance.

We conclude that hypoventilation during enflurane anaesthesia is not only a result of central respiratory depression, but also a function of awake airways resistance.

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INFLUENCE DE LA RESISTANCE DES PASSAGES D'AIR ET MODALITES VENTILATOIRES SUR LA Pa_{CO_2} PENDANT UNE ANESTHESIE A L'ENFLURANE

RESUME

On a mesuré sur 21 témoins adultes en bonne santé ayant subi une prémédication, pendant une anesthésie à l'enflurane et 60 ou 66% de protoxyde d'azote dans l'oxygène: le volume courant, la fréquence respiratoire et la Pa_{CO_2}. L'augmentation de la Pa_{CO_2} a été en corrélation avec la

valeur de FEV_1/VC déterminée avant l'anesthésie. Pendant l'anesthésie, la Pa_{CO_2} été en corrélation avec un indice de la résistance des passages d'air (FEV_1/taille) et elle a été influencée par les modalités de la respiration. Ces corrélations sont similaires à celles qui ont été signalées pour l'halothane.

EINWIRKUNG DES ATEMWIDERSTANDES UND DES VENTILATORISCHEN RHYTHMUS AUF Pa_{CO_2} WÄHREND EINER ENFLURANNARKOSE

ZUSAMMENFASSUNG

Strömungsvolumen, Atmungsfrequenz und Pa_{CO_2} wurden in 21 gesunden Erwachsenen mit Prämedikation während einer Enflurannarkose mit 60 oder 66% Stickoxyd in Sauerstoff gemessen. Das Anwachsen von Pa_{CO_2} stand in Wechselbeziehung mit den Werten von FEV_1/VC, vor der Narkose festgestellt. Pa_{CO_2} stand während der Narkose in Wechselbeziehung mit einem Atemwiderstandsindex FEV_1/Grösse) und war vom Atmungsrhythmus beeinflusst. Diese Wechselbeziehungen ähneln denen, die von Halothan berichtet wurden.

INFLUENCIA EJERCIDA POR LA RESISTENCIA DE LAS VIAS RESPIRATORIAS Y TIPO DE VENTILACION SOBRE EL Pa_{CO_2} DURANTE LA ANESTESIA DE ENFLURANO

SUMARIO

Se midió el volúmen de marea, frecuencia respiratoria y Pa_{CO_2} en 21 adultos sanos, premedicados, durante anestesia con enflurano y 60 o 66% de óxido nitroso en oxígeno. El aumento en el Pa_{CO_2} se correlacionó con el valor de FEV_1/VC, determinado antes de la anestesia. El Pa_{CO_2} durante la anestesia se correlacionó con un índice de resistencia en las vías respiratorias (FEV_1/altura) y fue influenciado por el tipo de respiración. Estas correlaciones son semejantes a aquellas presentadas para halotano.

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EFFECT OF PREANAESTHETIC MEDICATION ON ETOMIDATE

M. ZACHARIAS, J. W. DUNDEE, R. S. J. CLARKE AND J. E. HEGARTY

SUMMARY

The effects of diazepam and pethidine, when given as preanaesthetic medication, on the induction of anaesthesia and the postanaesthetic sequelae following etomidate were studied in women undergoing minor gynaecological procedures. Pain on injection was present in all the groups. However, the frequency was significantly less with the polyethylene glycol and propylene glycol formulations of the drug compared with the aqueous solution. A fast injection and pethidine premedication decreased the frequency also. The high frequency of excitatory phenomena in unpremedicated patients was decreased significantly by premedication with diazepam and pethidine, especially the latter. Respiratory and cardiovascular effects of the drug were not major problems. The frequency of emetic sequelae was high. Recovery was rapid even in the groups receiving sedative premedication.

Pain on injection, excitatory effects and emetic sequelae have been noted following injection of etomidate (Doenicke et al., 1973; Holdcroft et al., 1976; Kay, 1976a, b; Hendry, Miller and Lees, 1977). Many attempts have been made to decrease the frequency of troublesome side-effects, for example, by the use of fentanyl or lignocaine in the solution (Kay, 1976a). A change of solvent from water to polyethylene glycol or propylene glycol has been used recently in an attempt to decrease the high frequency of pain on injection, with some success. Since it has been shown previously that suitable preanaesthetic medication can reduce the frequency of excitatory effects of i.v. anaesthetic agents (Dundee, 1965a) a study of the influence of preanaesthetic medication on etomidate has been undertaken.

METHODS

Women (age range 16–60 yr), undergoing minor gynaecological operations of short duration, were studied. As in our previous study (Zacharias et al., 1978) the three available formulations of etomidate (aqueous, in polyethylene glycol (PEG) and in propylene glycol (PG)) were evaluated at two speeds of injection, 1 mg s^{-1} and 2 mg s^{-1} (*slow* and *fast* speeds).

The patients were subdivided further into three groups, the first being unpremedicated, while the second group received diazepam 10 mg orally 1 h before the anaesthetic and the third group received pethidine 75 mg i.m. 1 h before the induction of anaesthesia. Anaesthesia was induced with etomidate 0.3 mg kg^{-1} and maintained with 70% nitrous oxide in oxygen and further doses of etomidate 2–4 mg were administered as required.

Large, antecubital veins were selected wherever possible and an indwelling needle facilitated repeated injections of the drug. Pain on injection was elicited by asking the question: "Is your arm comfortable?" during the injection.

The grading of anaesthesia, etc. was as described in the previous paper. Arterial pressure was recorded by auscultation at 1 min and thereafter every 3–4 min until the end of anaesthesia. The condition of the patient 2 min after the end of anaesthesia was classified as awake, or with or without jaw tone and protective reflexes ("protected" or "unprotected"). Patients were questioned at 1 h and 6 h after operation for emetic sequelae. At the 6-h visit the patients were asked if they would like the same anaesthetic should they again require a similar operation. At this time they were asked for their memory of specified preoperative events (Dundee et al., 1977).

Table I gives the number of patients in each group, with their mean age, weight and duration of anaesthesia. To obtain sufficiently large groups for analysis, factors other than those under consideration were not taken into account when analysing the data. This is justified by the comparability of the 18 sub-groups.

The findings in the different groups were compared using the 2×2 or 2×n (χ^2) contingency test, except for the grades of anaesthesia where the ridit transformation (Bross, 1958) was used.

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TABLE I. *Details of patients and duration of anaesthesia*

Premedication	Formulation of etomidate	Speed of injection	*n*	Age (yr)	Weight (kg)	Duration of anaesthesia (min)
None	Aqueous	Slow	20	31.2	60.6	10.1
	Aqueous	Fast	20	27.3	59.3	10.6
	PEG	Slow	30	32.7	54.9	8.1
	PEG	Fast	33	33.1	61.3	9.2
	PG	Slow	20	32.4	58.8	8.6
	PG	Fast	20	29.7	55.9	7.4
Diazepam 10 mg oral	Aqueous	Slow	23	35.3	62.1	7.7
	Aqueous	Fast	20	31.3	55.0	9.6
	PEG	Slow	24	30.9	56.7	6.3
	PEG	Fast	20	36.7	58.8	7.4
	PG	Slow	20	34.3	56.7	8.7
	PG	Fast	20	28.7	52.9	8.1
Pethidine 75 mg i.m.	Aqueous	Slow	20	36.2	56.8	10.2
	Aqueous	Fast	20	28.7	56.6	9.3
	PEG	Slow	24	28.0	59.5	9.9
	PEG	Fast	22	37.6	61.1	9.0
	PG	Slow	20	32.8	55.3	10.3
	PG	Fast	20	31.5	56.6	9.5

TABLE II. *Percentage frequency of induction side-effects and pain on injection in each group*

Premedication	Formulation of etomidate	Speed of injection	*n*	Pain on injection	Excitatory phenomena	Respiratory upset	Respiratory depression	Decrease in AP > 20 mm Hg
None	Aqueous	Slow	20	50	75	25	5	20
	Aqueous	Fast	20	40	70	30	10	0
	PEG	Slow	30	30	80	13	0	27
	PEG	Fast	33	24	82	9	3	12
	PG	Slow	20	35	85	20	5	5
	PG	Fast	20	25	95	30	5	15
Diazepam 10 mg oral	Aqueous	Slow	23	44	61	4	4	13
	Aqueous	Fast	20	40	60	20	5	10
	PEG	Slow	24	33	63	25	0	8
	PEG	Fast	20	25	60	5	5	25
	PG	Slow	20	35	80	15	10	0
	PG	Fast	20	10	75	5	5	0
Pethidine 75 mg. i.m.	Aqueous	Slow	20	35	45	10	10	35
	Aqueous	Fast	20	35	35	5	20	20
	PEG	Slow	24	29	46	14	24	39
	PEG	Fast	22	14	18	14	14	18
	PG	Slow	20	10	25	0	15	20
	PG	Fast	20	10	30	0	25	10

RESULTS

Pain on injection

The high frequency of pain on injection is demonstrated in table II. This varied from 50% in unpremedicated patients receiving the aqueous formulation of the drug slowly, to 10% in patients premedicated with pethidine and receiving PG formulation rapidly.

There was a significantly lower frequency of pain on injection (premedication and formulations pooled) with the faster rate of administration ($\chi^2 = 4.058$; $P < 0.05$). Also, there was a significantly lower frequency of pain on injection with both PEG and PG formulations of etomidate as compared with the aqueous formulation of the drug ($\chi^2 = 6.529$ and 10.184 respectively; $P < 0.025$ and < 0.005

respectively). Preanaesthetic medication with pethidine significantly reduced the frequency of pain ($\chi^2 = 3.874$; $P < 0.05$), whereas with diazepam premedication the decrease in pain was not statistically significant ($\chi^2 = 3.227$; $0.10 > P > 0.05$).

Figure 1 shows the various factors influencing pain on injection with etomidate. The use of organic solvents (PEG and PG), fast injection and opiate premedication, decreased the frequency of pain on injection.

Excitatory phenomena

The frequency of excitatory phenomena with etomidate was unaffected by the speed of injection or the use of the three different solvents. However, the frequency was influenced markedly by preanaesthetic medication (table II; fig. 2). It was reduced significantly by diazepam ($\chi^2 = 18.310$; $P < 0.0005$) and to a greater extent by premedication with pethidine ($\chi^2 = 91.982$; $P < 0.0005$). There was a statistically significant difference between the frequency with these two premedicants ($\chi^2 = 27.232$; $P < 0.0005$).

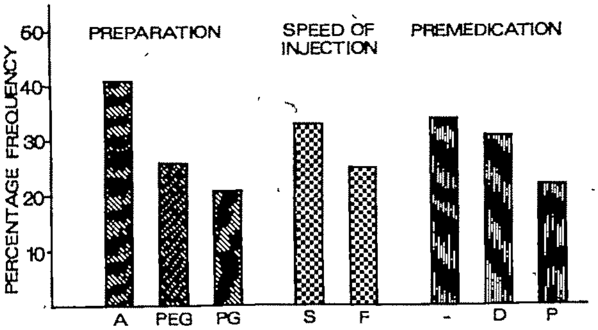

FIG. 1. Factors influencing pain on injection following etomidate. Aqueous (A), polyethylene glycol (PEG) and propylene glycol (PG) formulations of etomidate; Slow (S) and fast (F) speeds of injection; None (−), diazepam (D) and pethidine (P) preanaesthetic medications.

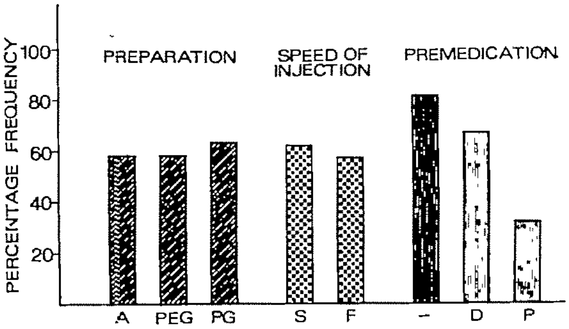

FIG. 2. Factors influencing the excitatory phenomena following etomidate. Abbreviations as in figure 1.

Respiratory and cardiovascular problems

Respiratory upset occurred in 0–25% of the patients and took the form of cough, hiccup and laryngospasm (table II). There was no difference related to the speed of injection or the formulation of the drug although there was a significant decrease following premedication with pethidine ($\chi^2 = 11.428$; $P < 0.001$). A

TABLE III. *Recovery characteristics in each group*

Premedication	Formulation of etomidate	Speed of injection	Emetic sequelae	Patient acceptability	Amnesic action	% patients awake or "protected" at 2 min
None	Aqueous	Slow	35	90	0	95
	Aqueous	Fast	40	85	10	100
	PEG	Slow	50	93	0	93
	PEG	Fast	39	94	0	88
	PG	Slow	45	95	0	100
	PG	Fast	40	100	5	100
Diazepam 10 mg oral	Aqueous	Slow	43	100	0	87
	Aqueous	Fast	50	100	0	100
	PEG	Slow	46	100	0	100
	PEG	Fast	50	100	0	100
	PG	Slow	35	90	0	95
	PG	Fast	35	90	0	100
Pethidine 75 mg i.m.	Aqueous	Slow	45	85	5	95
	Aqueous	Fast	55	90	10	95
	PEG	Slow	63	100	0	100
	PEG	Fast	55	96	0	91
	PG	Slow	35	95	5	90
	PG	Fast	45	100	0	95

lesser, but non-significant, decrease occurred following premedication with diazepam.

Apnoea of short duration occurred in a few patients but its frequency was not influenced by the speed of injection. It occurred least frequently with the PEG formulation. Premedication with pethidine increased significantly the frequency of apnoea compared with unpremedicated patients or those having diazepam premedication ($\chi^2 = 8.136$; $P<0.005$ and $\chi^2 = 7.965$; $P<0.005$ respectively).

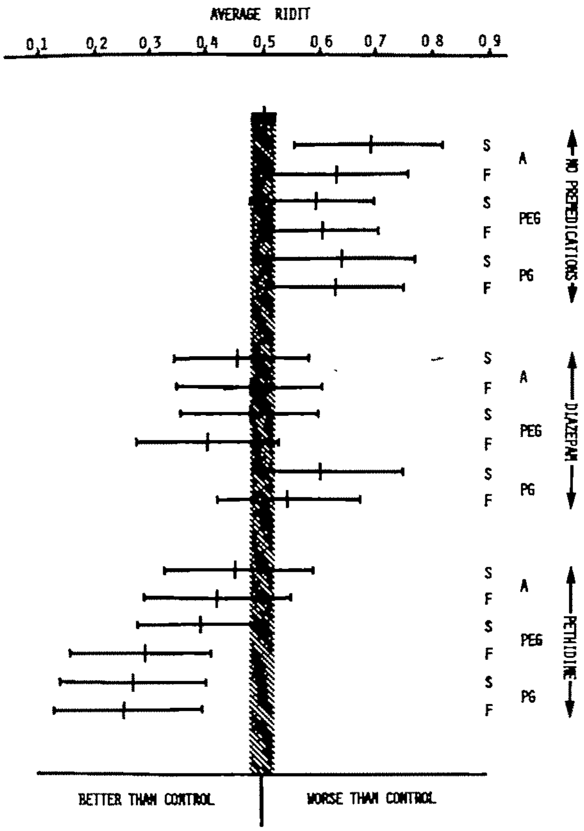

FIG. 3. Ridit analysis of grades of anaesthesia following etomidate. Shaded area = mean of pooled data ±2 standard errors. Lines indicate mean of each group ±2 SEM.

A decrease in systolic arterial pressure of more than 20 mm Hg occurred in a few patients, but it was of short duration. It was not influenced by the speed of injection but hypotension was observed more frequently when PEG formulation as compared with PG formulation was used ($\chi^2 = 6.195$; $P<0.025$). Premedication with pethidine induced a significantly higher frequency of hypotension compared with premedication using diazepam ($\chi^2 = 7.596$; $P<0.01$), though when compared with unpremedicated patients the difference was not statistically significant ($\chi^2 = 3.59$; $P>0.05$).

The ridit analysis of the various grades of anaesthesia within the different groups is presented in figure 3. Data from all the groups were pooled to obtain the "identified distribution" for the analysis and the various groups were then compared with it. The induction was smoother in the premedicated patients, especially when pethidine was used.

Recovery from anaesthesia was quick (table III) and a high percentage of patients were either awake or had jaw tone and protective reflexes at 2 min from the end of anaesthesia. There was no significant difference between the various groups ($\chi^2 = 18.790$; d.f. = 17; $P>0.05$).

Emetic sequalae

It was found that the speed of injection, formulation and premedication had no significant influence on the emetic sequelae ($\chi^2 = 9.173$; d.f. = 17; $P>0.05$) which were very frequent in all series (fig. 4).

In spite of the pain on injection and emetic sequelae the patient acceptability was high (table III) as judged by willingness to undergo the same anaesthetic again. There was no difference between the various groups ($\chi^2 = 19.641$; d.f. = 17; $P>0.05$).

There was no significant frequency of amnesia in any of the groups. Most patients had a clear memory of events such as the journey to the operating theatre and injection of the anaesthetic (table III).

DISCUSSION

Many attempts have been made to reduce the frequency of pain on injection associated with etomidate and a significant decrease in the frequency has been seen both in this study and when a fast injection has been given by others (Morgan, Lumley and Whitwam, 1975). It would seem likely that with the fast injection the irritant drug stayed in contact with the vein wall for a shorter time. The quicker onset of sleep with the faster injection may have prevented the patient from reporting the presence of pain.

A major attempt by the manufacturers of this drug to reduce this pain led to a change of the solvent of the drug from water to polyethylene glycol and propylene glycol. There was a statistically and clinically significant reduction of pain on injection with the newer formulations. The aqueous solution probably causes the pain mainly because of its acid pH (3.3) and the phosphate buffer which is needed to keep the solution

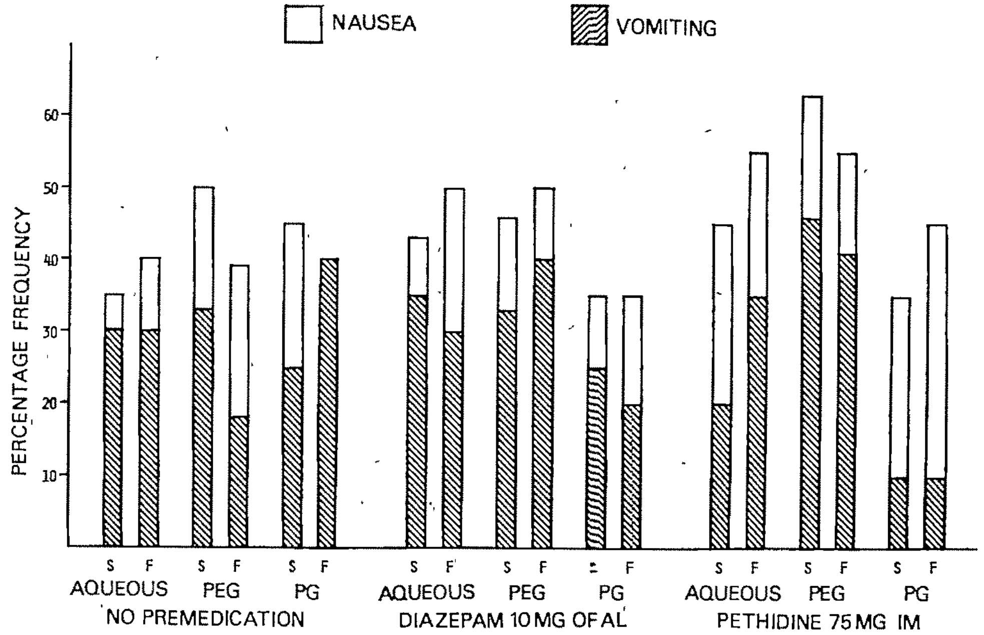

FIG. 4. Frequency of nausea and vomiting following etomidate. Abbreviations as in figure 1.

stable. The solutions in PEG and PG caused less pain, probably because of their lower acidity. However, this method of reducing the pain has not been as successful as was hoped. The effects of speed of injection and varying the solvent were not seen in the earlier study because of the small number of patients (Zacharias et al., 1978).

Preanaesthetic medication with pethidine reduced significantly the frequency of pain on injection, as one would expect. The reduction of pain observed with premedication using diazepam was probably a result of its sedative action, thereby making the patient more tolerant to minor degrees of pain. However, this reduction was not significant statistically.

Excitatory phenomena are perhaps the most important disadvantages of etomidate (Gooding and Corssen, 1976; Zacharias et al., 1978). Myoclonic movements, with or without hypertonus, make surgery difficult or even impossible and the frequency was as high as 80–90% in this study (table II). However, they disappeared gradually during the course of anaesthesia. These movements may be a result of overactivity of the subcortical centres and are a feature of many i.v. anaesthetics, such as methohexitone, propanidid, and even thiopentone under some circumstances (Dundee, 1965b). They are a property of the molecule so that a change of the formulation would not be expected to have much effect on it. A slower injection speed reduces the frequency of excitatory effects with methohexitone (Barron, 1968), but this was not seen with etomidate.

It is well known that suitable preanaesthetic medication decreases the excitatory effects of i.v. anaesthetics (Dundee, 1963). Diazepam acts by central sedation but opiates are even better in this respect as has been found with etomidate in the present study. In the current study the frequency of satisfactory grades of anaesthesia was much higher following premedication with pethidine.

Cough and hiccup were not as frequent with etomidate as with methohexitone (Dundee, 1963) and were decreased significantly by opiate premedication, probably as a result of the analgesic and sedative effects of the premedication. Respiratory depression in the form of apnoea of short duration was seen on occasions with etomidate, and could be explained by a central depressant action of the drug. This effect was potentiated by opiate premedication, and a significant increase in the frequency of apnoea was observed in that group.

Hypotension of significant severity does not occur with etomidate (Doenicke et al., 1974; Hendry, Miller and Lees, 1977). However, a decrease in systolic arterial pressure has been seen in a small percentage of patients receiving opiate premedication. An increase in peripheral blood flow produced by etomidate (Hempelmann et al., 1974) is probably the cause of the decrease in arterial pressure and as this occurs also with pethidine one would expect potentiation.

Recovery was rapid after etomidate (table III). This is a result of the rapid redistribution of the drug (Heykants et al., 1975) although metabolism is rapid also initially. Detailed studies on recovery from the drug are in progress. There was a high frequency of emetic sequelae, perhaps partly because minor gynaecological procedures themselves are associated with this. However, the emetic sequelae following etomidate mainly take the form of emergence vomiting. Opiate premedication increased the frequency, though this was not statistically significant. It is well known that, unfortunately, opiates increase the emetic sequelae after other i.v. anaesthetics (Dundee, Nicholl and Moore, 1962).

It was interesting to note that a large proportion of patients said that they would be prepared to have the same anaesthetic again. They were not asked whether there were any disagreeable features to the anaesthetic, which might have been a more discriminating question. However, the same question has been used previously to distinguish between the views expressed by patients of ketamine and methohexitone (Knox et al., 1970) and elicited a 29% acceptance of the former compared with 83% of the latter. The reason for the high patient acceptance might have been that in most instances the pain on injection was mild, with vomiting during emergence from anaesthesia, and there was complete and rapid recovery leaving the patient with a clear head. There were no unpleasant dreams or amnesia following its administration in the dosage described.

Therefore, it may be concluded that preanaesthetic medication, especially with an opiate, could make etomidate more acceptable clinically, although the unpleasant emetic effects persist.

ACKNOWLEDGEMENTS

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EFFET D'UN MEDICAMENT PREANESTHESIANT SUR L'ETOMIDATE

RESUME

On a étudié sur des femmes devant subir des interventions chirurgicales gynécologiques mineures, les effets du diazépam et de la péthidine, administrés en tant que médicaments préanesthésiants, sur l'induction de l'anesthésie et sur les séquelles post-anesthésiques après administration d'étomidate. On a constaté dans tous les groupes une douleur au moment de l'injection. Cependant, la fréquence a été moindre avec les formules de ces médicaments qui étaent basées sur le polyéthylène glycol et sur le propylène glycol qu'avec celles basées sur des solutions aqueuses. L'injection rapide et une prémédication de péthidine ont aussi fait diminuer la fréquence. La fréquence élevée des phénomènes excitatoires sur les patientes auxquelles on n'avait administré aucune prémédication a diminué d'une manière significative après prémédication de diazépam et de péthidine, surtout cette dernière. Les effets respiratoires et cardiovasculaires du médicament n'ont causé aucun problème majeur. La fréquence des séquelles émétiques a été élevée. La récupération a été rapide même chez les groupes qui avaient reçu une prémédication sédative.

AUSWIRKUNG VON PRAMEDIKATION AUF ETOMIDAT

ZUSAMMENFASSUNG

Die Auswirkung von Diazepam und Pethidin als Prämedikationsmittel auf des Einsetzen von Narkose und auf postnarkotische Folgeerscheinungen nach Verabreichung von Etomidat wurde bei Frauen mit kleineren gynäkologischen Operationen untersucht. Schmerz bei der Injektion war bei allen Gruppen gegeben. Wesentlich geringer war jedoch die Häufigkeit, wenn die Droge nicht als wässrige Lösung, sondern in ihrer Polyäthylen-Glykol- oder Propylen-Glykolformel verabreicht wurde. Schnelle Injektion und Prämedikation mit Pethidin verringerten ebenfalls die Häufigkeit. Die hohe Häufigkeit erregender Phänomene bei nicht vorbehandelten Patientinnen sank bei Prämedikation mit Diazepam und Pethidin stark ab, besonders bei letzterer Droge. Respiratorische und kardiovaskuläre Wirkungen der Droge waren kein besonderes Problem. Die Häufigkeit emetischer Folgeerscheinungen war hoch. Erwachen erfolgte schnell selbst in den Gruppen, die mit Sedativa vorbehandelt worden waren.

EFECTO EJERCIDO POR LA MEDICACION ANESTESICA SOBRE LA ETOMIDATA

SUMARIO

Se estudiaron los efectos ejercidos por diazepam y petidina, administrados en calidad de medicaciones preanestésicas, sobre la inducción de anestesia y la secuela postanestésica que siguió a la etomidata en mujeres sometidas a procedimientos ginecológicos menores. La inyección produjo dolor en todos los grupos. Sin embargo, la frecuencia disminuyó significativamente con las formulaciones de polietilenglicol y propilenglicol de la droga, en comparación con la solución acuosa. Lo que también disminuyó la frecuencia fue la aplicación rápida de la inyección, con premedicación de petidina. La gran frecuencia del fenómeno excitativo en pacientes no premedicados fue disminuida significativamente con premedicación de diazepam y petidina, especialmente ésta última. Los efectos respiratorios y cardiovasculares de la droga no causaron grandes problemas. La frecuencia de secuela emética resultó elevada. La recuperación fue rápida aún en aquellos grupos que recibieron premedicación sedativa.

Br. J. Anaesth. (1979), **51**, 135

ETOMIDATE FOR INDUCTION OF ANAESTHESIA AT CAESAREAN SECTION: COMPARISON WITH THIOPENTONE

J. W. DOWNING, R. J. R. BULEY, J. G. BROCK-UTNE AND P. C. HOULTON

SUMMARY

Thirty mothers undergoing elective Caesarean section received thiopentone 3.5 mg kg^{-1} and 30 received etomidate 0.3 mg kg^{-1} for induction of anaesthesia. Subsequent management of anaesthesia was identical in both groups. Maternal to fetal base excess differences and the degree of biochemical correlation between mother and infant were more favourable following etomidate than following thiopentone. The clinical status of the newborn was considered superior with etomidate.

Thiopentone is a standard induction agent in obstetric anaesthesia (Bradford and Moir, 1969; Baraka et al., 1971; Peltz and Sinclair, 1973; Downing et al., 1976; Mahomedy et al., 1976). However, barbiturates cause some degree of cardiorespiratory depression, influencing maternal–fetal haemodynamics and transplacental exchange (Dundee and Wyant, 1974). Thiopentone crosses the placental barrier and drug-induced depression of the newborn may result if a large dose is given to the mother (Finster and Poppers, 1968).

It has been suggested that current investigations of various induction agents for Caesarean section are inappropriate in view of the extremely low frequency of drug-induced neonatal depression at elective section (Crawford, 1977). However, these considerations may not apply if the fetus is at risk.

Etomidate, the new imidazole i.v. induction agent, has an action rapid in onset and of short duration. There is minimal alteration in cardiorespiratory function and recovery is uneventful (Morgan, Lumley and Whitwam, 1975; Fragen, Caldwell and Brunner, 1976). It does not cause detectable histamine release (Doenicke et al., 1973). Initially, etomidate possessed two undesirable side-effects: pain on injection and excessive involuntary movements during induction. The introduction of a new preparation of etomidate (Hendry, Miller and Lees, 1977) and the use of a rapid induction sequence (Downing et al., 1974) has reduced the frequency of both problems.

We describe the use of etomidate for anaesthesia at Caesarean section. The results are contrasted with those obtained from a control series receiving thiopentone (Buley et al., 1977).

PATIENTS AND METHODS

Sixty mothers who conformed to the criteria of the "clinically acceptable ideal case" (Crawford, 1962) gave consent to the investigation. The patients were not in labour and the membranes were intact. In every patient, placental function was judged to be normal on clinical grounds. Gestational age was 38–42 weeks, confirmed by a positive foam test and an amniotic fluid lecithin–sphyngomyelin ratio greater than 2.5; the fetus was a singleton with vertex presenting. The mother lay on her left side during transfer to the operating theatre for elective Caesarean section.

During anaesthesia and surgery a 15° foam rubber wedge was placed under the right buttock, providing left lateral tilt. A standard anaesthetic technique was used similar to that described by Buley and others (1977). In 30 mothers, etomidate was used as the i.v. induction agent in a dose of 0.3 mg kg^{-1} and the remaining 30 received thiopentone 3.5 mg kg^{-1} (control series). The control series includes 23 patients described in our previous report (Buley et al., 1977).

Patients weighing more than 85 kg were excluded from the trial and the dose of the induction agent related to weight was not corrected for pregnancy. Tracheal intubation was facilitated by the simultaneous administration of suxamethonium 1.75 mg kg^{-1} or [illegible] mg kg^{-1} with thiopentone or etomidate from the same syringe (Downing et al., 1974). Manual pressure was applied to the cricoid cartilage by an assistant until the tracheal tube cuff was inflated.

Ventilation of the lungs was controlled using a Manley ventilator delivering an expired minute

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volume of 130 ml kg^{-1} designed to maintain maternal Pa_{CO_2} within a range 3.7–4.8 kPa.

Anaesthesia was maintained with 50% nitrous oxide in oxygen (monitored with an Ohio Airco Model 600 Oxygen Analyser) and enflurane 0.5–0.8%. Further muscle relaxation was provided by i.v. injection of pancuronium 2–4 mg. Following delivery of the infant, pethidine 50 mg was administered i.v. The residual effects of the non-depolarizing drug were antagonized at the end of the procedure with neostigmine 5 mg mixed with atropine 1.2 mg i.v. (Brock-Utne et al., 1978).

At the time of delivery maternal arterial and fetal umbilical cord blood samples were obtained and analysed using an IL 413 blood-gas analyser. Results were verified using a Radiometer B.M.S. Mk II blood-gas apparatus. The electrodes were calibrated using standard buffer solutions and certified gases or a Radiometer gas-mixing device. Base excess values were calculated. Student's *t* test for unpaired data was used in analysing the results. In calculating fetal base excess values, corrections were made for the degree of haemoglobin desaturation in the umbilical cord blood samples (Buley et al., 1977).

RESULTS

Mothers

The average maternal age of the etomidate group (23.9 yr, SEM 1.0) was younger than that of the thiopentone control group (26.8 yr, SEM 0.5) ($P<0.05$). The mean body weights of the two groups were comparable; etomidate 71.6 kg, SEM 1.9, *v.* thiopentone 70.0 kg, SEM 1.9.

The arterial blood-gas status of the mothers at delivery (table I) showed respiratory alkalosis with a compensatory metabolic acidosis (more marked in the etomidate group ($P<0.005$)) in the majority at delivery.

TABLE I. *Maternal arterial (Ma) blood-gas and acid–base values at delivery (mean ± SEM) in patients receiving thiopentone with nitrous oxide, oxygen and enflurane or etomidate with nitrous oxide, oxygen and enflurane*

	Group				
	Thiopentone		Etomidate		
	Mean	SEM	Mean	SEM	Significance
[H+] (nmol litre^{-1})	39.2	0.9	41.7	0.6	$P<0.05$
P_{CO_2} (kPa)	4.23	0.06	4.16	0.05	n.s.
P_{O_2} (kPa)	23.7	1.3	22.4	1.1	n.s.
Base excess (mmol litre^{-1})	−3.6	0.5	−5.6	0.3	$P<0.005$

n.s. = not significant.

Infants

The average induction to delivery (I–D) and uterine incision to delivery (U–D) intervals were similar in both groups (table II). The time to sustained breathing (TSR) by the infants was slightly shorter with etomidate ($0.1>P>0.05$), but much shorter than in our previously published left lateral tilt series (TSR thiopentone: left tilt 27.3 s ± 5.7 *v.* etomidate 10.8 s ± 1.5 ($P<0.005$)) (Buley et al., 1977). Apgar scores at 1, 2 and 5 min were similar (table II), a mild degree of neonatal depression (A – C 4–6) being encountered in the first 2 min of life in only three infants of the two groups.

The acid–base and blood-gas values obtained from

TABLE II. *Time intervals and clinical status of the infants whose mothers received thiopentone with nitrous oxide, oxygen and enflurane or etomidate with nitrous oxide, oxygen and enflurane. (Mean ± SEM)*

	Thiopentone			Etomidate			
	Mean	SEM		Mean	SEM		Significance
I–D (min)	10.1	0.6		10.5	0.5		n.s.
U–D (s)	61.5	5.9		56.8	5.4		n.s.
TSR (s)	19.6	4.4		10.8	1.5		$0.1<P<0.05$*
Apgar score	1 min	2 min	5 min	1 min	2 min	5 min	
1–3	0	0	0	0	0	0	n.s.
4–6	1	0	0	1	2	0	n.s.
7–8	29	30	30	29	28	30	n.s.

*Original thiopentone left lateral tilt series (Buley et al., 1977); 27.3 s (± SEM 5.7) *v.* 10.8 s (± SEM 1.5) etomidate, $P<0.005$.

TABLE III. *Comparison of umbilical venous (Uv) and arterial (Ua) biochemical values, of infants whose mothers received either thiopentone with nitrous oxide, oxygen and enflurane or etomidate with nitrous oxide, oxygen and enflurane. (Mean ± SEM)*

	Group				
	Thiopentone		Etomidate		
	Mean	SEM	Mean	SEM	Significance
$[H^+]$ (nmol litre^{-1})					
Uv	45.3	1.1	47.6	0.6	n.s.
Ua	51.0	1.3	53.3	0.7	n.s.
$P\mathrm{CO}_2$(kPa)					
Uv	5.34	0.1	5.33	0.09	n.s.
Ua	6.42	0.14	6.43	0.12	n.s.
$P\mathrm{O}_2$ (kPa)					
Uv	4.4	0.17	4.30	0.10	n.s.
Ua	2.66	0.14	2.68	0.08	n.s.
O_2 saturation (%)					
Uv	71.9	2.8	71.1	1.6	n.s.
Ua	39.9	3.2	39.3	2.1	n.s.
Base excess (mmol litre^{-1})					
Uv	−4.7	0.7	−6.5	0.3	$P<0.05$
Ua	−6.8	0.7	−8.0	0.3	n.s.

n.s. = not significant.

the umbilical venous (Uv) and arterial (Ua) blood samples in the thiopentone and etomidate groups are compared in table III. There was a relatively greater degree of metabolic acidosis in the infants whose mothers received etomidate.

TABLE IV. *Maternal arterial to umbilical venous Δ(Ma − Uv) and umbilical arterial Δ(Ma − Ua) differences in women who received either thiopentone with nitrous oxide, oxygen and enflurane or etomidate with nitrous oxide, oxygen and enflurane. (Mean ± SEM)*

	Thiopentone		Etomidate		
	Mean	SEM	Mean	SEM	Significance
$[H^+]$ (nmol litre^{-1})					
Δ(Ma − Uv)	6.1	0.6	5.9	±0.5	n.s.
Δ(Ma − Ua)	11.8	0.9	11.6	±0.8	n.s.
$P\mathrm{CO}_2$ (kPa)					
Δ(Ma − Uv)	1.12	0.9	1.17	±0.08	n.s.
Δ(Ma − Ua)	2.19	0.13	2.27	±0.11	n.s.
Base excess (mmol litre^{-1})					
Δ(Ma − Uv)	2.3	0.2	1.3	±0.2	$P<0.001$
Δ(Ma − Ua)	3.7	0.3	2.8	±0.3	$P<0.05$

n.s. = not significant.

Blood-gas and acid–base differences between mother and fetus Δ(Ma − Ua) and Δ(Ma − Uv) are presented in table IV. BE values are significantly smaller for etomidate than for thiopentone.

Umbilical venous to arterial differences Δ(Uv − Ua) representing the fetal internal environment (Dawes, Mott and Widdicombe, 1974) were similar with both drugs.

Biochemical interrelationships

Correlation coefficients (*r*) for maternal arterial *v.* fetal blood-gas results are shown in table V. The expected close correlation between Ma and Ua hydrogen ion concentration $[H^+]$ and base excess (BE) values was not seen with etomidate. However, *r* values for Ma *v.* Uv/Ua $P\mathrm{CO}_2$ were greater with etomidate. With etomidate, a negative correlation emerged between Ma and Δ(Ma − Uv)/Δ(Ma − Ua) $[H^+]$ and an unusual relationship was apparent between Ma and Δ(Ma − Ua) BE.

TABLE V. *Correlation coefficients (r) for maternal v. fetal blood-gas results in groups receiving either thiopentone with nitrous oxide, oxygen and enflurane or etomidate with nitrous oxide, oxygen and enflurane*

Ma *v.*	Thiopentone	Etomidate
$[H^+]$		
Uv	0.83***	0.61***
Ua	0.76***	0.24
Δ(Ma − Uv)	0.08	−0.45*
Δ(Ma − Ua)	0.17	−0.52**
$P\mathrm{CO}_2$		
Uv	0.46*	0.58***
Ua	0.31	0.50**
Δ(Ma − Uv)	−0.11	0.01
Δ(Ma − Ua)	−0.08	0.05
Base excess		
Uv	0.77***	0.65***
Ua	0.73***	0.31
Δ(Ma − Uv)	0.02	0.16
Δ(Ma − Ua)	−0.09	0.47**

Significance (d.f. = 28): *$P<0.05$; **$P<0.005$; ***$P<0.001$.

DISCUSSION

The first clinical trials of etomidate were encouraging (Doenicke et al., 1973; Morgan, Lumley and Whitman, 1975), and, in view of the increasing number of adverse reactions associated with the administration of other i.v. induction agents (Dundee, 1976), the drug could represent a useful addition to the obstetric anaesthetist's armamentarium.

Etomidate produces rapid anaesthesia in one arm-brain circulation time and, unlike thiopentone, it is hydrolysed rapidly to an inactive substance so that recovery is faster than that following barbiturates (Hendry, Miller and Lees, 1977; Lees and Hendry, 1977).

Etomidate causes minimal alteration in the cardiorespiratory state (Morgan, Lumley and Whitwam, 1975; Fragen, Caldwell and Brunner, 1976; Gooding and Corssen, 1976), and does not appear to release histamine in detectable quantities (Doenicke et al., 1973).

The advent of a new polyethyleneglycol solvent for etomidate has decreased significantly the frequency of pain on i.v. injection (Hendry, Miller and Lees, 1977), and our routine induction technique for Caesarean section (Downing et al., 1974) allows little time for excess movement at induction to be a problem.

Mother and fetus

Both groups of patients in this study were placed in the left lateral tilt position (Buley et al., 1977). Although the mothers in the etomidate group were younger on average than the control patients, the mean parity in the two series was comparable. Any advantage accruing to the infants of the etomidate group because of maternal age differences should be offset by the relatively greater degree of maternal acidaemia present in the etomidate group.

Unfortunately, blood-gas and acid–base measurements obtained from the umbilical vessels are indicative of the fetal biochemical state only at the time of sampling, and, although our programme attempted to ensure that the only difference in the two groups was the induction agent, we should not disregard other factors which may influence maternal to fetal exchange.

Preoperative placental function is important in this regard, but clinical data did not indicate any major differences between the groups. Blood flow through the uterus and placenta is impeded during uterine contraction and is influenced by posture. None of our patients was in labour and the effects of posture on chorio-decidual haemodynamics (Downing et al., 1974; Buley et al., 1977) were standardized. Surgical interference and rupture of the membranes also disturb fetal blood-gas homeostasis and this can be difficult to evaluate (Fothergill, Robertson and Bond, 1971). However, all the Caesarean sections were performed by the same group of surgeons using the same technique, as indicated by the similar I–D and U–D intervals in both groups.

Fetal state at delivery, as indicated by Ua sample (Dawes, Mott and Widdicombe, 1954; James et al., 1958), was similar in both groups, except for the decrease in Uv BE with etomidate. When the blood-gas status of the mother is related specifically to the fetal state using the indices $\Delta(\text{Ma}-\text{Uv})$ and $\Delta(\text{Ma}-\text{Ua})$, etomidate would appear to provide advantages over thiopentone. This was not reflected in the Apgar scores at 1 min. Marx, Mahajan and Miclat (1977) have demonstrated that a correlation exists between the Ua sample and the (A – C) Apgar score only at the moment of birth. The clinical impression that the etomidate group of infants responded more favourably to introduction to the outside environment was reflected to some extent by differences in the time to spontaneous respiration.

To evaluate further the cause of this improved fetal tissue perfusion, we examined the effect of etomidate on the biochemical state of umbilical venous (Uv) blood. There was an improvement in Uv BE of the etomidate group. Furthermore, the $\Delta(\text{Ma}-\text{Uv})$ BE difference was significantly smaller with etomidate than with thiopentone. Thus there would appear to be improved matching of maternal to placental circulation after the administration of etomidate. This statement is supported further by the close correlation between Ma *v.* Uv/Ua $P\text{CO}_2$ with etomidate.

The absence of a correlation between Ma and Ua $[\text{H}^+]$ and BE in the etomidate series, coupled with the emergence of a significant negative relationship, Ma *v.* $\Delta(\text{Ma}-\text{Uv})/\Delta(\text{Ma}-\text{Ua})$ $[\text{H}^+]$ and the positive correlation noted for Ma *v.* $\Delta(\text{Ma}-\text{Ua})$ BE (table V) with etomidate, deserves further comment. On pharmacological grounds, fetal cardiovascular haemodynamics and organ perfusion should be maintained better following the injection of etomidate, relative to thiopentone. This may improve the transport of fetal circulating fixed acids to the placenta.

A review of the literature reveals that no induction agent investigated for Caesarean section has proved manifestly superior to thiopentone (Bradford and Moir, 1969; Baraka et al., 1971; Peltz and Sinclair, 1973; Downing et al., 1976; Mahomedy et al., 1976; Crawford, 1977). Indeed, James and others (1977) and Magno (1976) were unable to recommend lumbar extradural analgesia over a thiopentone, nitrous oxide, oxygen, volatile agent and relaxant anaesthesia for Caesarean section.

Our study of etomidate suggests that this drug may be of particular value in obstetric anaesthesia, especially in the clinically ill fetus whose biochemical status may be served better. Further testing of this hypothesis is indicated.

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ETOMIDATE POUR INDUCTION DE L'ANESTHESIE LORS D'UNE OPERATION CESARIENNE: COMPARAISON AVEC LE THIOPENTONE

RESUME

Trente mères devant subir une opération césarienne à froid ont reçu 3,5 mg kg^{-1} de thiopentone, alors que 30 autres recevaient 0,3 mg kg^{-1} d'étomidate pour l'induction de l'anesthésie. La conduite ultérieure de l'anesthésie a autrement été identique dans les deux cas. Les différences excédentaires de la base entre la mère et l'enfant ainsi que le degré de corrélation biochimique entre la mère et l'enfant ont été plus favorables après l'étomidate qu'après la thiopentone. Le statut clinique du nouveau-né a été considéré comme étant meilleur avec l'étomidate.

ETOMIDAT ZUR EINLEITUNG DER NARKOSE FÜR KAISERSCHNITT: EIN VERGLEICH MIT THIOPENTON

ZUSAMMENFASSUNG

Von 60 Müttern, die sich für einen Kaiserschnitt entschieden hatten, erhielten 30 3,5 mg kg^{-1} Thiopenton und 30 0,3 mg kg^{-1} Etomidat zur Einführung der Narkose. Danach wurde die Narkose in beiden Gruppen identisch weitergeführt. Die von der Mutter zum Fötus übergehenden basalen, unterschiedlichen Überschüsse und der Grad der biochemischen Wechselbeziehung zwischen Mutter und Kind waren nach Etomidat günstiger als nach Thiopenton. Der klinische Zustand der Neugeborenen wurde nach Etomidat für überlegen ergehalten.

ETOMIDATA PARA LA INDUCCION DE ANESTESIA EN SECCION CESAREA: COMPARACION CON TIOPENTONA

SUMARIO

Treinta madres sometidas a sección cesárea electiva recibieron 3,5 mg kg^{-1} de tiopentona y 30 recibieron 0,3 mg kg^{-1} de etomidata para inducción de anestesia. La administración posterior de anestesia fue idéntica para ambos grupos. Las diferencias entre el exceso básico materno y fetal y el grado de correlación bioquímica entre madre e infante fueron más favorables tras la administración de etomidata que tras la administración de tiopentona. El estado clínico del recién nacido fue considerado superior con etomidata.

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EFFECTS OF ENFLURANE ANAESTHESIA AND SURGERY ON ENDOCRINE FUNCTION IN MAN

T. Oyama, K. Taniguchi, H. Ishihara, A. Matsuki, A. Maeda, T. Murakawa and T. Kudo

SUMMARY

Forty-five patients underwent enflurane anaesthesia and surgery. Anaesthesia alone evoked little change in the plasma concentrations of ACTH, cortisol or antidiuretic hormone (ADH), but there were significant increases during surgery. The plasma concentrations of aldosterone increased during anaesthesia alone, and a further increase was noted during surgery. Neither enflurane anaesthesia nor surgery significantly influenced plasma concentrations of renin activity and thyroxine. A significant decrease in the plasma triiodothyronine concentration was detected during anaesthesia alone, and a further decrease was found during and following surgery. Enflurane anaesthesia did not affect the plasma concentration of luteinizing hormone (LH) in male subjects throughout surgery, but a significant decrease in female patients was detected to the first day after operation. The plasma concentrations of testosterone decreased during anaesthesia alone and surgery, and a further decrease was noted on the first day after operation.

Much attention has been paid to the effects of anaesthesia and surgery on endocrine function. Although some effects of enflurane on endocrine function have been reported previously by us (Oyama, Matsuki and Kudo, 1972) and by Dobkin and his colleagues (1968), the information about the effects of enflurane anaesthesia and surgery on pituitary, adrenal, thyroid and gonadal function has been meagre. The present study was undertaken to determine the plasma concentrations of ACTH, cortisol, aldosterone, antidiuretic hormone (ADH), thyroxine (T_4), triiodothyronine (T_3), luteinizing hormone (LH) and testosterone throughout the period of enflurane anaesthesia and surgery, and on the first day after operation.

METHODS

Forty-five patients, ranging in age from 18 to 62 yr, were studied after giving informed consent. The physical status of these patients was ASA classification I or II. None had a history of endocrine disease or of hepatic or renal malfunction. They were divided into three groups: group I comprised 15 patients, in whom anterior pituitary and adrenocortical function were studied by determining the plasma concentrations of ACTH, cortisol and aldosterone. Group II consisted of 20 female patients who underwent abdominal surgery, in whom posterior pituitary, thyroid and gonadal functions were studied by determining the plasma concentrations of antidiuretic hormone (ADH), thyroxine (T_4) and triiodothyronine (T_3), and luteinizing hormone (LH). Group III consisted of 10 male patients who underwent non-abdominal surgery, in whom gonadal function was studied by determining the plasma concentrations of testosterone and luteinizing hormone (LH).

The patient's routine medication was withheld during the 12 h preceding surgery, and food and water intake was restrained for 10 h before the induction of anaesthesia. Premedication consisted of pentobarbitone 100 mg orally, pethidine 35 mg i.m., and atropine 0.5 mg i.m. Because of diurnal variations of the plasma concentrations of hormones, induction of anaesthesia was started at 8.30 a.m.

Anaesthesia was induced with thiopentone sodium which was followed by suxamethonium 40 mg to facilitate tracheal intubation. Anaesthesia was maintained with enflurane 1.0–3.0% combined with 50% nitrous oxide in oxygen, using an Ethrantec vaporizer. Anaesthesia alone continued for at least 45 min in group I and for 30 min in groups II and III, respectively.

Anaesthesia was maintained at light to moderate levels as judged by clinical signs including respiration, heart rate and arterial pressure, and by periodic analysis of arterial concentrations of enflurane measured by gas chromatography. Intermittent

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positive pressure ventilation of the lungs was continued manually throughout anaesthesia and surgery. Tubocurarine 3–6 mg was injected when muscle relaxation was required. Fluid was administered during anaesthesia and surgery as follows.

Group I. Low mol. wt. dextran 500 ml, then lactated Ringer's solution, was infused at a constant rate of 200 ml h^{-1}, started immediately before the induction of anaesthesia and continued until the patient had recovered adequately from anaesthesia in the recovery room. In addition, blood was transfused in 11 patients in whom blood loss was estimated to be more than 300 g.

Groups II and III. Lactated Ringer's solution, 10 ml kg^{-1} h^{-1}, was infused immediately before the induction of anaesthesia until 2 h after the start of anaesthesia; thereafter the infusion rate was reduced to 7–8 ml kg^{-1} h^{-1} until the patient had recovered adequately from anaesthesia in the recovery room. In addition, blood was transfused in seven patients, in whom blood loss was estimated at more than 400 g. On the first day after operation water intake in 20 female patients of group II ranged from 1000 to 3000 ml per day (mean 1675 ml).

Six millilitre of venous blood was withdrawn for determination of plasma concentrations of ACTH, cortisol and aldosterone; 10 ml for T_4, T_3, ADH, LH and osmolality; and 2 ml for testosterone and LH determinations.

Blood sampling times were: group I: (1) 5 min before the induction of anaesthesia, for a control value; (2) on three occasions during 45 min of enflurane anaesthesia alone; (3) on two occasions during the surgical procedure; (4) in the recovery room when the patient had awakened adequately. Groups II and III: (1) control sampling as in group I; (2) 30 min after enflurane anaesthesia alone; (3) 10 min after the start of surgery (only ADH analysis); (4) 1 h after the start of surgery; (5) in the recovery room when the patient had awakened adequately; and (6) 24 h later.

After the induction of anaesthesia urine was collected through an indwelling catheter. Measurement of urine osmolality was made at the corresponding sampling time specified for venous blood, except for 10 min after the start of surgery. The plasma was separated immediately and kept frozen (−20 °C) until the concentrations of hormones could be determined. Except for cortisol these were measured by radioimmunoassay. ACTH was determined according to the method of Berson and Yalow (1968), using the Radiochemical-Centre-ACTH-Kit. Recovery rate was 40%, and the coefficient of variation (c.v.) was 12%. Plasma cortisol was determined by Rudd's spectrophotometric method (Rudd, Sampson and Brooke, 1963); the recovery rate was 102%. Plasma renin activity (PRA) was measured by the method of Haber and colleagues (1969), using the PRA-RIA-Kit (CEA-IRE-SORIN); recovery rate was 72% and c.v. was 7%. Plasma aldosterone was determined by the method of Mayes and colleagues (1970); recovery rate was 68% and c.v. was 6%. Plasma ADH was measured by the method of Husain and colleagues (1973); recovery rate was 74% and c.v. was 11%. Plasma concentrations of T_4 were analysed using the Dainabbott-RIA-Kit, similar to the method of Chopra (1972), and c.v. was 3%; T_3 was analysed by the similar method of Mitsuma and colleagues (1976), using the Dainabbott-RIA-Kit, and c.v. was 2.7%. Plasma LH was determined by Midgley's method (1966), and c.v. was 6.8%. Plasma testosterone was measured by the method of Furuyama, Mayes and Nugent (1970), using testosterone-RIA-Kit (CEA-IRE-SORIN); the c.v. was 7.4%.

Serial e.c.g. tracing and arterial gas analysis revealed

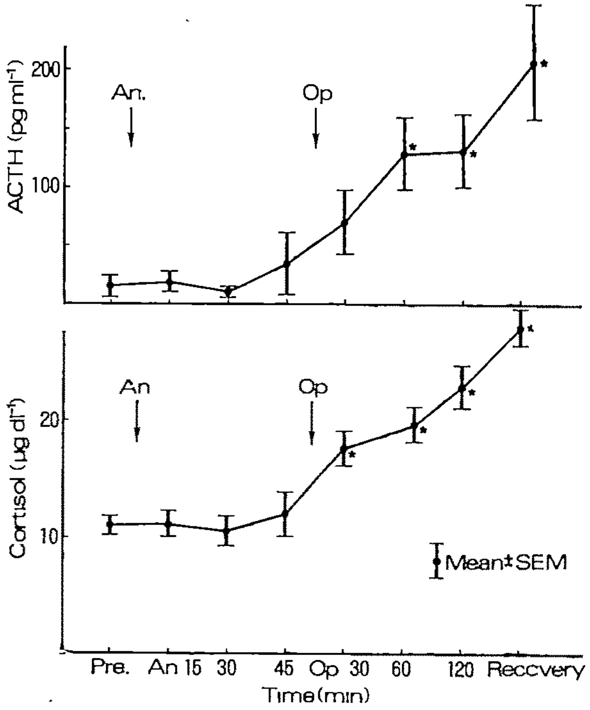

FIG. 1. Plasma ACTH and cortisol concentrations during and after enflurane anaesthesia and surgery in man. Pre. = before induction; An. = anaesthesia; Op. = operation; $*P < 0.05$ compared with value before induction.

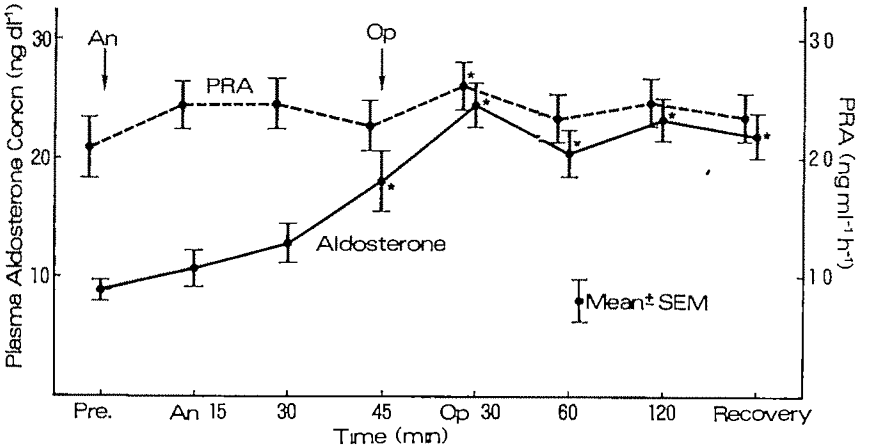

FIG. 2. Plasma concentrations of aldosterone and plasma renin activity (PRA) during and after enflurane anaesthesia and surgery in man. Abbreviations as figure 1. $*P < 0.05$ compared with value before induction.

no remarkable abnormalities of circulatory or respiratory function throughout the procedure. Student's *t* test was used for the statistical analyses.

RESULTS

During anaesthesia alone plasma concentrations of ACTH increased, but not significantly compared with the control value. Surgery evoked a significant increase in ACTH concentration 1 and 2 h after the start of surgery. The highest concentrations were recorded when the patient had recovered adequately from anaesthesia in the recovery room as demonstrated in figure 1.

Plasma cortisol did not change significantly during anaesthesia alone, while surgery increased it significantly. Plasma cortisol remained increased until the patient had recovered adequately from anaesthesia in the recovery room (fig. 1). Plasma aldosterone concentrations increased, but without statistical significance during the first 30 min of anaesthesia alone compared with control values. However, the value increased 2 times over the preinduction control after 45 min of anaesthesia alone. A further increase in aldosterone concentration occurred during surgery, and in the recovery room (fig. 2).

Plasma renin activity (PRA) did not vary appreciably throughout the procedure in comparison with control, except for the value at 30 min after the start of operation (30% increase (fig. 2)).

The plasma ADH concentration did not increase 30 min after the start of anaesthesia alone. Surgical stress evoked significant increases, especially 10 min after the skin incision. Thereafter it remained increased, but decreased slightly toward preinduction value. On the first day after operation the plasma concentration of ADH returned to the preinduction control value (fig. 3).

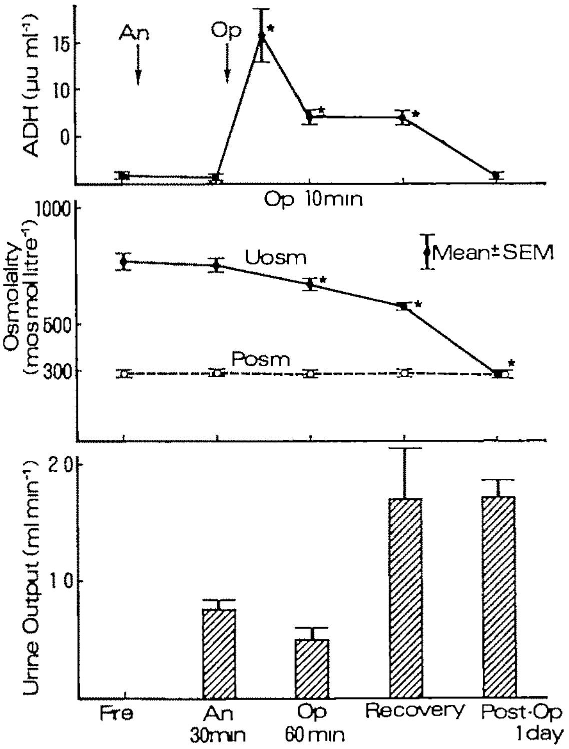

FIG. 3. Renal function and plasma ADH concentration during and after enflurane anaesthesia and surgery in man. Uosm = osmolality of urine; Posm = osmolality of plasma; $*P < 0.05$ compared with value before induction. Other abbreviations as figure 1.

Serum osmolality did not change throughout the procedure. The urine osmolality decreased gradually and the lowest values were recorded on the first day after operation (37% of the control value). Urine output decreased during anaesthesia alone, and was reduced further to 75% of the control value during 1 h after the start of surgery; thereafter a significant increase was noted.

Plasma concentrations of T_4 did not change during enflurane anaesthesia or surgery. However, T_4 decreased significantly to 70% of the control value on the first day after operation. Plasma T_3 decreased to 74% and 79% of the control value at 30 min after the start of anaesthesia and 1 h after the start of surgery. A further significant reduction (to 71%) continued to the first day after operation (tables I and II).

TABLE I. *Plasma thyroxine* (T_4) ($\mu g\ dl^{-1}$) *during enflurane anaesthesia and surgery*

Patient	Pre-ind.	Anaesth. 30 min	Surgery 60 min	RR	Post-op. 1 day
1	6.1	7.8	10.5	9.7	4.4
2	8.5	6.9	7.5	5.2	3.7
3	6.6	6.0	7.5	4.6	3.6
4	7.7	9.0	15.5	8.5	4.4
5	8.5	7.5	10.0	5.5	5.0
6	4.7	7.2	6.5	6.5	4.8
7	10.0	9.0	7.2	6.5	8.5
8	3.8	4.5	5.0	2.3	2.7
9	7.6	8.0	7.9	8.7	6.2
10	7.0	5.0	7.5	7.9	4.8
11	5.6	5.0	4.7	7.2	4.7
12	4.1	3.0	2.7	2.7	2.7
13	4.5	5.0	4.4	4.1	4.4
14	8.0	7.3	7.9	5.2	5.6
15	7.0	8.5	7.8	7.3	4.9
16	8.5	5.4	9.2	6.9	5.0
17	9.9	9.0	10.7	4.0	4.2
18	6.5	7.3	8.0	5.4	6.2
19	8.4	6.2	6.6	10.2	−1.0
20	8.5	11.7	13.8	9.2	8.4
Mean	7.1	7.0	8.0	6.4	5.0
SEM	0.4	0.4	0.7	0.5	0.3
P		n.s.	n.s.	n.s.	< 0.001

RR = when the patient had recovered adequately from anaesthesia in the recovery room; n.s. = not significant.

TABLE II. *Plasma triiodothyronine* (T_3) ($ng\ ml^{-1}$) *during enflurane anaesthesia and surgery*

Patient	Pre-ind.	Anaesth. 30 min	Surgery 60 min	RR	Post-op. 1 day
1	0.80	0.76	0.74	0.78	0.68
2	1.40	1.15	0.78	1.00	0.54
3	1.15	0.74	0.64	0.44	0.64
4	1.05	1.15	0.82	1.00	0.88
5	1.55	1.50	1.80	1.10	1.50
6	1.60	1.00	1.05	0.98	1.35
7	1.20	1.35	1.20	0.80	0.89
8	1.05	1.25	1.78	1.15	0.54
9	0.62	0.61	1.05	1.30	0.92
10	0.64	0.53	0.63	0.50	0.49
11	0.73	0.68	0.50	0.68	0.76
12	0.84	0.54	0.62	0.54	0.46
13	1.20	0.68	0.73	0.74	1.00
14	1.55	0.90	1.85	2.00	1.40
15	1.45	0.66	1.05	0.66	0.78
16	1.20	0.74	0.90	0.82	0.48
17	1.20	0.62	0.70	0.94	0.66
18	1.65	0.70	1.10	0.70	0.74
19	1.10	0.63	0.68	0.53	−1.00
20	1.25	0.92	0.82	0.93	1.10
Mean	1.16	0.86	0.92	0.88	0.83
SEM	0.07	0.06	0.08	0.08	0.07
P		< 0.01	< 0.01	< 0.01	< 0.01

RR = when the patient had recovered adequately from anaesthesia in the recovery room.

Plasma concentrations of LH in male patients did not change significantly during anaesthesia alone or surgery (fig. 4). In female subjects, LH decreased to 84% of control at 30 min after anaesthesia, and there was a continued decline to 75% on the first day after operation (fig. 4). Plasma testosterone decreased to 86% and 87%, at 30 min after the start of anaesthesia and 1 h after surgery. A further significant reduction to 49% of control continued to the first day after operation (fig. 4).

DISCUSSION

Our data demonstrated that plasma concentrations of *ACTH and cortisol* remained unchanged during enflurane anaesthesia alone. However, they were increased during surgical stress. Changes in plasma concentrations of ACTH correlated well with those of cortisol. The present results confirmed a previous report of plasma cortisol concentrations (Oyama et al., 1972), although Dobkin and others (1968) observed that plasma cortisol concentrations increased after 30 min during enflurane anaesthesia alone in man. The effects of enflurane anaesthesia alone on plasma concentrations of ACTH and cortisol differ from those of diethyl-ether, halothane and neuroleptanaesthesia, which increased plasma ACTH and cortisol concentrations (Oyama et al., 1968, 1972; Oyama and Takiguchi, 1970). The findings of the present study imply that enflurane anaesthesia does not stimulate the glucocorticoid component of pituitary–adrenocortical function. Therefore, from a theoretical point

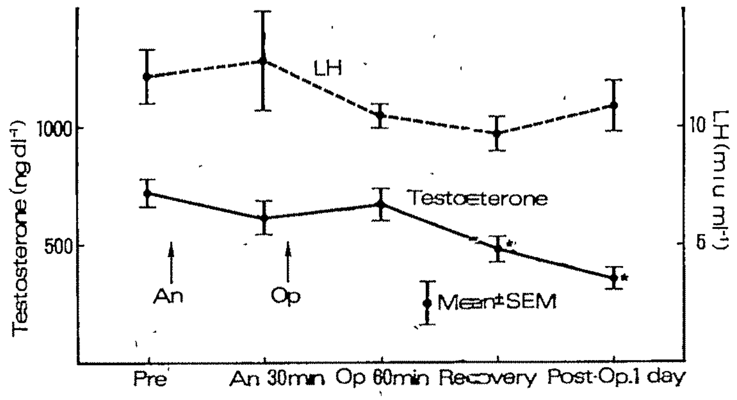

FIG. 4. Plasma LH and testosterone concentrations during and after enflurane anaesthesia and surgery in male subjects. $^*P < 0.05$ compared with values before induction. Abbreviations as figure 1.

of view, enflurane anaesthesia is recommended in patients with hyperadrenocortical function such as in Cushing's syndrome.

Aldosterone indirectly conserves the intravascular fluid volume and plays an important role in maintaining fluid and electrolyte homeostasis. Plasma aldosterone concentrations showed a two- and three-fold increase during enflurane anaesthesia and surgery, respectively. Our present findings are similar to those concerning other volatile agents including halothane, diethyl-ether and methoxyflurane, which increased plasma aldosterone concentrations (Oyama et al., 1978).

The plasma concentrations of aldosterone during stress appear to be regulated mainly by aldosterone secretion from the adrenal cortex. Aldosterone secretion is primarily controlled by the renin–angiotensin system, and ACTH has only a secondary role in aldosterone secretion under non-stressful conditions. However, our present data demonstrated that plasma renin activity did not change markedly during enflurane anaesthesia or surgery, except for the value at 30 min after the start of surgery, and that plasma concentrations of ACTH were increased significantly during surgery. Several investigators (Naruse, 1971; Robertson and Michelakis, 1972; Miller et al., 1975) questioned the participation of the renin–angiotensin system in the increased plasma aldosterone concentrations during anaesthesia and the early phase of the surgical procedure.

It appears that the increase in the plasma concentrations of aldosterone depends on plasma ACTH rather than on renin activity during enflurane anaesthesia and surgery. The adrenocortical response to enflurane anaesthesia judged by plasma concentrations of aldosterone would be different from that as judged by plasma cortisol concentrations. We consider that this agent may be used safely for patients with aldosterone hypersecretion, such as primary aldosteronism (Matsuki et al., 1976).

It is documented that the increased secretion of *antidiuretic hormone* (*ADH*) from the posterior pituitary gland plays an important role in oliguria during anaesthesia and surgery (Moran et al., 1964). Various factors are attributable to the release of ADH from the posterior pituitary gland (Schreier and Berl, 1975). Oyama and Kimura (1970) and Oyama, Sato and Kimura (1971) demonstrated that various anaesthetic agents including diethyl-ether and halothane significantly increased the plasma concentrations of ADH in man. The volume of fluid administered appears to modify both ADH release and renal function during anaesthesia and surgery (Ishihara, 1977).

Enflurane anaesthesia alone did not increase ADH concentrations. This contrasts with the effects of other agents, such as diethyl-ether, halothane, methoxyflurane, thiopentone and droperidol–fentanyl (Oyama and Kimura, 1970; Oyama and Sato, 1970; Oyama, Sato and Kimura, 1971; Ishida, 1977) which increased plasma concentrations of ADH during anaesthesia alone in man. Significant increases in plasma ADH were found 10 min after skin incision during enflurane anaesthesia. This appears to be evoked by visceral stimulation, and confirms a previous report (Ukai, Moran and Zimmerman, 1968). The plasma concentrations of ADH returned to preinduction values on the first day after operation. Our data indicated that enflurane anaesthesia does not affect ADH release from the posterior pituitary gland. Therefore, from a theoretical point of view, enflurane anaesthesia could be recommended in patients with inappropriate ADH release, such as dehydrated patients, although ADH release might be influenced more markedly by surgical stress.

Our data demonstrated that no remarkable change in the plasma concentration of *thyroxine* (T_4) was detected during enflurane anaesthesia, as observed similarly during methoxyflurane, Althesin and thiopentone–nitrous oxide anaesthesia (Oyama, 1973; Oyama et al., 1975), whereas diethyl-ether, halothane and isoflurane increased plasma concentrations of T_4 (Oyama, 1973; Oyama et al., 1975). However, Brandt and colleagues (1976) reported that plasma concentrations of T_4 increased to about 125% of control values 1 h after skin incision under enflurane–nitrous oxide anaesthesia in man. It is difficult to speculate on the reason for this discrepancy. The difference in the method of analysis of plasma T_4, and in administration of enflurane might contribute in part to the results.

Triiodothyronine (T_3) is known to be five times as potent biologically as T_4 (Larsen, 1972). Plasma T_3 decreased to 74% compared with control during enflurane anaesthesia alone, and a further reduction was observed during surgery, which demonstrated a pattern similar to that observed during other types of general anaesthesia (Matsuki et al., 1978). Although the precise mechanism of the decrease in plasma T_3 following anaesthesia remains unknown, the following factors are postulated to contribute to a reduction in T_3 concentrations. (1) Decrease in T_3 release from the thyroid gland; (2) inhibition of conversion of T_4 to T_3 in the extrathyroid tissues; (3) increase in T_3 uptake in the peripheral tissues; (4) the half-life of T_3 (about 7 h). Matsuki and colleagues (1978) demonstrated that plasma concentrations of T_3 were reduced more markedly during major than during minor surgery. They suggested that the decreased peripheral conversion from T_4 to T_3 was chiefly responsible for this decline, and disturbed hepatic function during anaesthesia and surgery might play an additional role. The change in T_3 or T_4 occurs independent of pituitary stimulation (Macdonald, Chapman and Franklin, 1976). Our data imply that enflurane anaesthesia did not stimulate thyroid function, judged by plasma concentration of T_4 or T_3. Therefore, enflurane anaesthesia may be an anaesthetic of choice for patients with hyperthyroidism.

Luteinizing hormone secreted from the pituitary gland enhances the synthesis and secretion of sex hormones including progesterone, testosterone and oestrogen. Enflurane anaesthesia alone for 30 min did not change the plasma concentrations of LH in male subjects, while in female subjects a significant decrease in the LH concentration (20%) was noted 30 min after enflurane anaesthesia alone. Although variation in the concentrations recognized depends upon the follicular, luteal or post-menopausal phase, a similar declining pattern in the plasma LH concentrations was observed in patients regardless of the phase of the menstrual cycle during anaesthesia.

Enflurane differs from halothane, which causes an increase in plasma LH in man (Oyama, Aoki and Kudo, 1972). Surgical stress also failed to increase plasma LH during enflurane anaesthesia in both male and female subjects. Surgical stress would be expected to evoke transient increases in plasma LH in male subjects at the beginning of surgical procedures unless the operation is minor (Aono et al., 1972; Oyama et al., 1977). Stimulation of pituitary LH secretion appears to increase the plasma concentrations of LH during halothane, thiopentone, Althesin and ketamine anaesthesia and surgery (Oyama, Aoki and Kudo, 1972; Oyama and Kudo, 1972; Oyama, Maeda and Kudo, 1975; Oyama et al., 1977). It is difficult to speculate on the mechanism of the decreased LH values of female subjects during enflurane anaesthesia and surgery. Oestrogen and progesterone might affect the feed-back mechanism of the hypothalamo–pituitary–gonadal axis in female subjects.

A decrease in the plasma concentrations of *testosterone* during enflurane anaesthesia alone and surgery in the present study follows the similar tendency with other anaesthetic agents such as halothane and thiopentone (Oyama, Aoki and Kudo, 1972; Oyama and Kudo, 1972). It is suggested that direct depression of testosterone secretion by anaesthesia or through decreased sensitivity to LH, or both, might account for the decreased plasma concentrations of testosterone during anaesthesia. The remarkable decline in the plasma concentrations of testosterone in the period following surgery could be related to depression of secretion of LH. Anaesthesia and surgery may lead to decreased plasma concentrations of anabolic steroid hormone, which might contribute to protein catabolism after operation.

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EFFETS DE L'ANESTHESIE PAR L'ENFLURANE ET DE LA CHIRURGIE SUR LA FONCTION ENDOCRINIENNE DE L'HOMME

RESUME

Quarante-cinq malades ont été soumis à une anesthésie par l'enflurane puis à une intervention chirurgicale. L'anesthésie seule n'a provoqué que peu de changements dans les concentrations d'ACTH, de cortisol ou d'hormone antidiurétique (ADH) dans le plasma, mais il y en a eu des augmentations significatives pendant l'intervention. Les concentrations d'aldostérone dans le plasma ont augmenté pendant l'anesthésie seule, et on en a remarqué une autre augmentation pendant l'opération. Ni l'anesthésie par l'enflurane ni l'intervention chirurgicale n'ont influencé d'une manière significative les concentrations de l'activité rénine et de la thyroxine dans le plasma. Une diminution importante des concentrations de triiodothyronine dans le plasma a été décelée pendant l'anesthésie seule et une autre diminution a été constatée pendant et après l'intervention. L'anesthésie par l'enflurane n'a pas affecté la concentration d'hormone progestinogène (LH) dans le plasma des sujets mâles pendant l'ensemble de l'opération mais on en a constaté une baisse importante chez les femmes jusqu'au lendemain de l'opération. Les concentrations de testostérone dans le plasma ont baissé pendant l'anesthésie seule et pendant l'opération, et une autre baisse a été remarquée le lendemain de l'opération.

DIE AUSWIRKUNGEN EINER ENFLURAN-NARKOSE UND EINES CHIRURGISCHEN EINGRIFFES AUF DIE ENDOKRINE FUNKTION

ZUSAMMENFASSUNG

Fünfundvierzig Patienten unterzogen sich einer Enfluran-narkose und einem chirurgischen Eingriff. Die Narkose allein bewirkte geringe Veränderungen der Plasmakonzentrationen von ACTH, Cortisol oder ADH, doch kam es während der Operation zu wesentlichen Anstiegen. Die Plasmakonzentrationen von Aldosteron stiegen allein während der Narkose, und es kam zu einem weiteren Anstieg während der Operation. Die Plasmakonzentrationen von Renin und Thyroxin wurden weder durch Enflurannarkose noch durch die Operation wesentlich beeinflusst. Ein wesentliches Sinken der Konzentrationen von Trijodothyronin wurde allein während der Narkose beobachtet, ein weiteres Absinken während und nach der Operation. Enflurannarkose beeinflusste nicht die Konzentration des luteinisierenden Hormons (LH) bei männlichen Patienten während des Eingriffes, doch kam es bei Patientinnen bis zum ersten Tag nach der Operation zu einem wesentlichen Sinken der Konzentration. Die Plasmakonzentrationen von Testosteron sanken sowohl während Narkose als auch während der Operation, und ein weiteres Sinken ergab sich am ersten Tag nach der Operation.

EFECTOS EJERCIDOS POR ANESTESIA DE ENFLURANO Y CIRUGIA SOBRE LA FUNCION ENDOCRINA EN EL HOMBRE

SUMARIO

Se sometieron 45 pacientes a anestesia de enflurano y cirugía. La anestesia sola evocó poco cambio en las concentraciones de ACTH, cortisol u hormona antidiurética (ADH), pero no se produjeron aumentos significativos durante la cirugía. Las concentraciones de aldosterona en la plasma aumentaron durante la anestesia sola, y se notó un aumento adicional durante la cirugía. Ni la anestesia de enflurano, ni la cirugía influenciaron significativamente las concentraciones de la actividad de renina y tiroxina. Se detectó una significativa disminución en las concentraciones de triyodotironina en la plasma durante la anestesia sola, y se observó una disminución adicional durante la cirugía posterior. La anestesia de enflurano no afectó la concentración de la hormona luteinizante (LH) en los sujetos masculinos durante la cirugía, pero se detectó una significativa disminución entre las mujeres pacientes hasta el primer día después de la operación. Las concentraciones de testosterona en la plasma disminuyeron durante la anestesia sola y cirugía, y se notó otra reducción más en el primer día después de la operación.

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ARRHYTHMIA DURING ORAL SURGERY: FASCICULAR BLOCKS IN THE CARDIAC CONDUCTING SYSTEM

J. P. ALEXANDER AND J. G. MURTAGH

SUMMARY

Two hundred and four patients were monitored during oral surgery using three surface e.c.g. leads simultaneously. In nine patients, sustained supraventricular tachycardia was observed during surgical stimulation. The role of sympathetic stimulation and halothane anaesthesia in producing arrhythmia is discussed.

Cardiac arrhythmia occurs commonly during oral surgery under general anaesthesia (Kaufmann, 1966; Ryder, 1970; Ryder and Townsend, 1974). The interpretation of these disturbances of cardiac function, particularly the more bizarre rhythms, has remained in doubt. One opinion (Alexander, 1971) is that they are supraventricular or A–V junctional in origin, while others disagree (Ryder, Charlton and Gorman, 1973). Rollason and Hall (1973) discussed the significance of dangerous ventricular arrhythmia, and Green and Coplans (1973) mention multifocal ventricular extrasystoles. This paper presents the findings of a more detailed electrocardiographic study.

METHOD

Two hundred and four patients (38 female) were studied in the supine position. The ages ranged from 10 to 71 yr; 22 were older than 50 yr. Twelve patients were known to have heart disease. The operations were for exodontia and usually lasted 60 min or longer. Premedication was with atropine 0.6 mg i.m. given 1 h before surgery.

Anaesthesia was induced with methohexitone 1–1.5 mg kg^{-1} followed by suxamethonium 50 mg (30 patients), diazepam 10 mg (126 patients (Hudson, 1974)), or non-paralysing doses of pancuronium (0.03 mg kg^{-1} in 10 patients) or fazadinium (0.3 mg kg^{-1} in 38 patients) to aid naso-tracheal intubation. The throat was packed and anaesthesia with spontaneous respiration continued using halothane (2% reducing to 1% or less from a Fluotec vaporizer) in a mixture of 66% nitrous oxide in oxygen. Either a Magill or a Bain circuit was used with total gas flows of 100 ml kg^{-1} min^{-1}.

Cardiac rhythm was monitored continuously using a Cardien type 141 oscilloscope (Cardiac Recorders Ltd) linked to three isolated e.c.g. modules (one type 142D with ratemeter, two type 155). The internal connections of this arrangement were modified to permit the display of any three e.c.g. signals from a single input (Appendix) and recordings were made when desired with an ultraviolet S.E. oscillograph type 3006 (S.E. Labs (E.M.I.) Ltd) on Linograph Direct Print paper type 1895 (Kodak).

Leads II, aVF and V_1 or leads I, II and V_1 were employed for monitoring.

Arterial blood was taken for gas analysis in heparinized syringes from 16 patients before operation and from 158 patients (78%) at the start and finish of surgery, and, when possible, when an arrhythmia occurred.

CARDIAC CONDUCTION

Before analysing the results, a brief summary of modern thoughts on the conducting system of the heart will be presented. The atrioventricular node (AVN) (fig. 1 (Krickler, 1974)) is divided into proximal (AN), central (N) and distal (NH) regions, the whole area often being called the A–V junction. The AN zone receives normal impulses from the sinoatrial (SA) node via three internodal tracts (INT). The middle (N) zone slows the impulse so that, at atrial rates exceeding 170 beat min^{-1}, varying degrees of block may occur, protecting the ventricles against overstimulation. The bundle of His (HB) is formed from the distal (NH) part and is said to divide into three discrete fascicles (possibly near its origin (James and Sherf, 1971)), the right bundle branch (RBB) and anterior (LAD) and posterior (LPD) divisions of the left bundle branch (LBB) (Rosenbaum, Elizari and Lazzari, 1970). Recent anatomical studies suggest that a centroseptal (CS) branch arises also

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from the LBB (Uhley, 1972). Conduction of impulses is slowed at the junction of the Purkinje network with the myocardium and physiological disturbances may block impulses at this location (Myerberg, Gelband and Hoffman, 1971). If cellular function is depressed, propagation of impulses may be impaired at some point in the conduction system, ultimately leading to blocking of the impulse or rendering the tissue partially or completely refractory to the next stimulus. The fibres of the AV node consist of two types, one with a long conduction time and a short refractory period (α), and the other with a short conduction time and a longer refractory period (β) (Moe, Preston and Burlington, 1956). Thus a premature impulse may be conducted down one pathway but not the other, which may later be able to conduct the impulse in a retrograde direction, thus setting up a reciprocal rhythm. Blocking or slowing of impulses in one or more of the conducting pathways may explain aberration of intraventricular conduction.

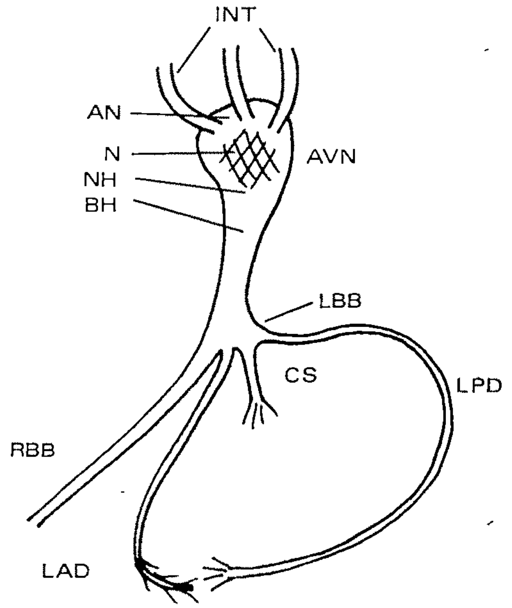

FIG. 1. Schematic representation of the cardiac conduction system. INT = internodal tracts; AVN = atrioventricular node, with proximal (AN), central (N) and distal (NH) regions and bundle of His (BH). LBB = left bundle branch, with posterior (LPD), anterior (LAD) and centroseptal (CS) divisions; RBB = right bundle branch.

Because of its length and small diameter, RBB would be expected to show physiological block (RBBB) most commonly, and this is indeed the case, followed in order by left anterior hemiblock (LAH) and, uncommonly, left posterior hemiblock (LPH) or complete left bundle branch block (LBBB). In patients with heart disease, LBBB occurs more frequently because of the proximity of the left bundle to the aortic valve and its involvement by ischaemic lesions, but still RBBB is commoner, resulting either from ischaemia or from stretching of the fascicle by ventricular hypertrophy.

THE FRONTAL-PLANE QRS AXIS

The frontal-plane axis (AQRS) can be determined from any two of the six frontal-plane e.c.g. leads. Figure 2 illustrates the reference system and the planes in which these six leads lie. The axis is found by calculating the mean deflection of the QRS complexes in each of the chosen leads and then determining the algebraic sum of these deflections. Using two leads, an accuracy of better than 15° is not normally possible. As an example, the first beat in figure 3 shows obvious negative deflections in both lead II and aVF and the sum of these indicates a mean axis of about −75°.

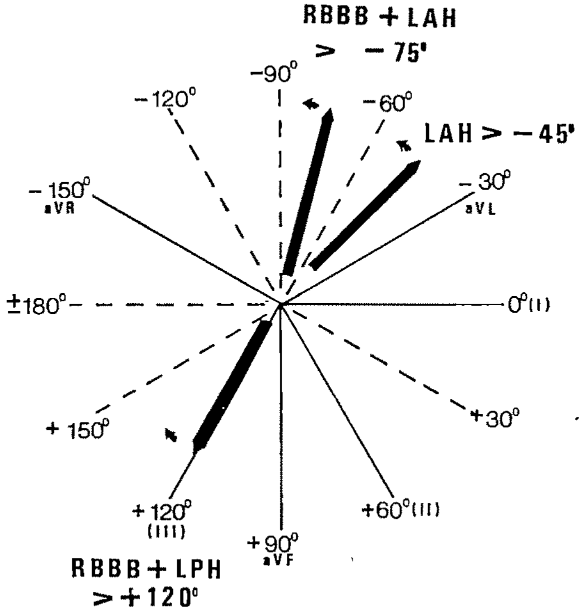

FIG. 2. The six-axial reference system. The frontal-plane leads are numbered clockwise (positive) or anti-clockwise (negative) with the number of degrees separating them from lead I. LBBB has an axis between −30° to +30°, RBBB between +60° and +120° (neither shown). LAH has an axis greater than −45°, RBBB+LAH greater than −75°, RBBB+LPH greater than +120°, LPH (not shown) greater than +110°.

The normal limits in adults are +90° to −30°: with RBBB (wide positive deflection in V_1) the axis usually lies at about +90°, while with LBBB (wide negative deflection in V_1) it lies at about −30°, both often being just within the normal limits of the axis, although there may be considerable variation. In figure 3, beat 3 (LBBB) has an axis of +80° and beat 4 (RBBB) an axis of −15°. LAH gives a negative or left-axis deviation of −45° or more and RBBB+LAH a negative axis of −75° or more (fig. 2). With RBBB+LPH there is right-axis deviation to +120° or more. It can be appreciated that a change from RBBB pattern (+90°) to RBBB+LAH will alter the electrical axis by nearly 180° and this is well illustrated by the bi-directional character of alternate complexes in leads II and aVF in figure 3. A detailed account of the electrical axis can be found in a recent paper by Rowlands (1978).

RESULTS

In all patients the heart rate increased after induction of anaesthesia with methohexitone (Bernhoff, Eklund and Kaijser, 1972) and there was a further increase during endotracheal intubation, to 150 beat min^{-1} or more in 33% of patients. Nine patients were noted to have ectopic beats during induction. The heart rate decreased when anaesthesia was established, but always increased when surgery commenced, and in 13% it again exceeded 150 beat min^{-1}. Fifteen different patients (of whom four were known to have heart disease) had occasional or frequent (> 20 min^{-1}) bigeminal ectopic complexes during surgery. A further nine different patients (table I) had bizarre arrhythmias (bi-directional tachycardia in at least one Standard lead) which were sustained for several minutes during surgery, and these nine form the basis of this report.

TABLE I. *Sustained arrhythmia during oral surgery*

Operation	No. of patients	Age (yr)
Buried canine	1	13
Extraction wisdom teeth	5	19, 24, 24, 24, 41
Dental clearance	3	38, 57, 69

Three e.c.g. recordings are reproduced (figs 3–5). The other six were similar in their interpretation. All showed supraventricular tachycardia (rates 120–220 beat min^{-1}) with bi-directional atrial (or A–V junctional) ectopic beats in leads I, II or aVF, and aberrant conduction in the ventricles. Changes in the AQRS indicated that RBBB or RBBB+LAH was common, while complete LBBB was seen less often and LPH rarely. Sometimes exact analysis was not possible where the block was incomplete. In figure 3, a regular pattern of RBBB alternating with RBBB+LAH is seen, apart from LBBB in the third beat. Slurring of the latter part of QRS in beats 2 and 4 in aVF (terminal delay) is typical of RBBB pattern. In figure 4, negative deflections with wide QRS in V_1

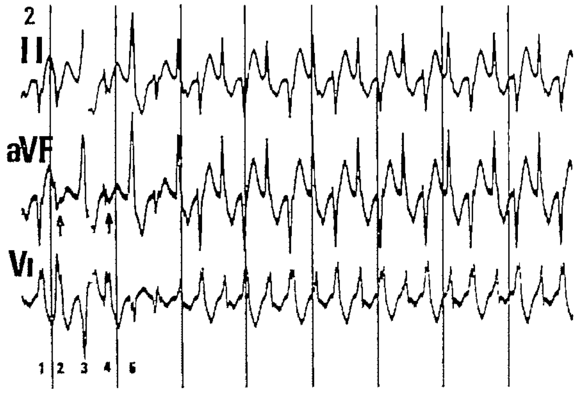

FIG. 3. Case 2. Male 24 yr, extraction of wisdom teeth. Leads II, aVF, V_1. Bi-directional tachycardia (170 beat min^{-1}) resulting from atrial ectopic beats with aberrant conduction in the ventricles. Frontal plane QRS axes in paratheses. Beat: 1. RBBB+LAH (−75°). 2. RBBB (+30°); 3. LBBB (+80°); 4. RBBB (−15°). The record settles to a constant pattern of RBBB (beat 4) alternating with RBBB+LAH (beat 5). Bidirectional in leads II and aVF. Note terminal delay of QRS in beats 2 and 4 in aVF (arrowed) which is characteristic of bundle branch block. Paper speed 25 mm s^{-1}; time lines are at 1-s intervals.

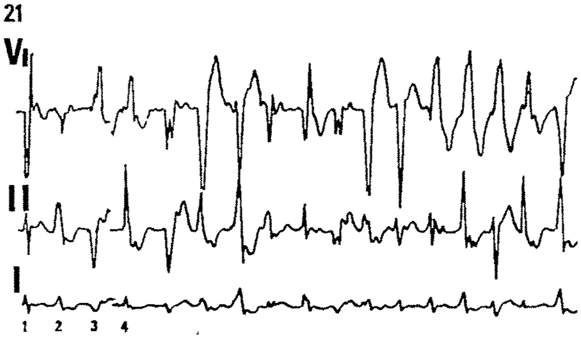

FIG. 4. Case 21. Male 24 yr, extraction of wisdom teeth. Leads V_1, II, I. Supraventricular tachycardia (180 beat min^{-1}), bi-directional ectopic beats with aberration. Beat: 1. RBBB with L axis deviation, possibly LAH (−45°); 2. LBBB (−60°); 3. RBBB+LAH (−75°); 4. Incomplete RBBB (+75°). The last three beats show RBBB+LAH (−75°), incomplete RBBB (+75°) and LBBB (+45°) in that order. (Retouched.)

TABLE II. *Comparison of mean arterial blood-gases (kPa); Magill or Bain circuits. P values are obtained from Student's t test. Individual results for patients during arrhythmia in parentheses*

Circuit and no. of patients	Start of surgery		End of surgery		During arrhythmia	
	Pa_{O_2} (kPa)	Pa_{CO_2} (kPa)	Pa_{O_2} (kPa)	Pa_{CO_2} (kPa)	Pa_{O_2} (kPa)	Pa_{CO_2} (kPa)
Magill, 66	21.4 ± 6.0	6.0 ± 0.8	19.7 ± 6.8	5.3 ± 0.8	16.9 (13.8, 29.2, 14.2, 10.1)	6.1 (4.8, 6.9, 7.7, 5.1)
Bain, 92	18.0 ± 5.7	6.3 ± 0.8	16.6 ± 4.5	5.8 ± 0.8	(10.9, 21.5)	(9.4, 5.7)
t	3.23	1.91	3.15	3.05		
P	< 0.005	$< 0.10 > 0.05$	< 0.005	< 0.005		

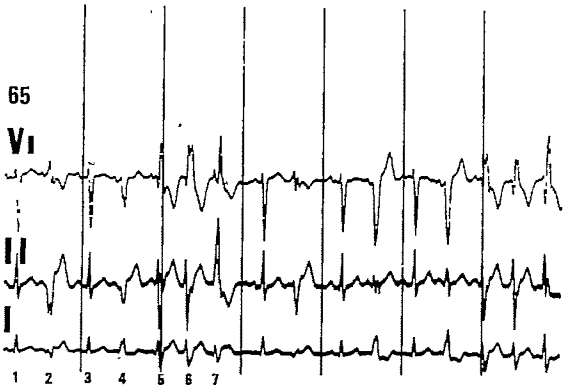

FIG. 5. Case 65. Male 19 yr, wisdom teeth. Leads V_1, II, I. Multiple atrial ectopic beats with varying degrees of ventricular aberration. Rate varies from 120 to 180 beat min^{-1}. Beat: 1. is normal (0°); 2. RBBB, possibly with LAH (−90°); 3. Normal (0°); 4. LBBB or LAH (L axis deviation, −60°); 5 and 6. RBBB, perhaps with LAH (−45°); 7. RBBB (+60°). The last complex shows RBBB (+45°), the two previous RBBB + LAH (−45°).

indicate frequent LBBB and the different depths of the deflections reflect the varying completeness of the blocks. In figure 5, at a lower rate, normal complexes are outnumbered by beats showing RBBB, LBBB and RBBB with left-axis deviation, which suggests RBBB + LAH.

Pa_{O_2} was significantly greater at the beginning of surgery when the Magill circuit was used, although Pa_{CO_2} measurements were not significantly different (table II). At the end of surgery there were larger Pa_{O_2} and smaller Pa_{CO_2} values with the Magill circuit compared with the Bain circuit using gas flows of 100 ml kg^{-1} min^{-1}. In patients who had arrhythmia resulting from conduction blocks, there was little difference in Pa_{CO_2} except for patient 65 (fig. 5) where, as a result of a technical fault in the gas supply, Pa_{O_2} 10.9 kPa and Pa_{CO_2} 9.4 kPa were recorded.

Systolic arterial pressures as determined by sphygmomanometry and palpation of the radial pulse were maintained at near normal values during the presence of arrhythmias, although there was an obvious pulse deficit with many of the abnormal beats. Direct arterial pressure recording in two patients confirmed that the mean arterial pressure was satisfactory although there was considerable variation in peak systolic pressure during arrhythmia.

DISCUSSION

A case of bi-directional tachycardia in a healthy young man undergoing oral surgery has been reported where an oesophageal electrode indicated that the most likely basis of the arrhythmia was supraventricular tachycardia with alternative aberration of the branches of the bundle of His (Alexander, Bekheit and Fletcher, 1972). However, the use of three suitable surface leads simultaneously allows better interpretation of ventricular performance and of alterations in the electrical axis of the heart (AQRS) in the frontal plane. Under the conditions of the present study (light halothane anaesthesia), 4.5% of patients responded to the stimulus of surgery with rapid heart rates mediated by an ectopic pacemaker in the A–V junctional tissue or bundle of His, to which the conducting tissues were unable to respond, so that intermittent bundle branch block patterns appeared. This type of arrhythmia may be confused with one having a ventricular origin (Sandler and Marriott, 1965).

These patients usually had normal heart rates before induction of anaesthesia, and responded to induction with sinus tachycardia of 120–150 beat min^{-1}, suggesting release of sympathetic control previously dominated by parasympathetic tone (Taggart et al., 1976), with possibly increased circulating concentrations of catecholamines (Edmondson, Roscoe and Vickers, 1972).

The frequency of fascicular block in our patients agrees with the findings of Rosenbaum, Elizari and Lazzari (1970), who suggested that the right bundle branch and left anterior division are more labile. This indicates that right bundle branch block and left anterior hemiblock occur most often, while left posterior hemiblock and complete left bundle branch block are uncommon, reflecting the anatomical and physiological features of these structures. Impulses which traverse the fascicles when they are partially refractory can give rise to varying degrees of aberration of intraventricular conduction. Gotta and others (1976) considered that aberrant conduction was a precursor of serious cardiac arrhythmia during halothane anaesthesia for oral surgery.

Numerous studies have demonstrated that halothane depresses myocardial contractility in animals (Brodkin, Goldberg and Kayne, 1967; Hashimoto, Endoh and Kimura, 1975; Merin, Verdouw and de Jong, 1977) and in man (Prys-Roberts et al., 1972). In canine experiments Reynolds, Chiz and Pasquet (1970) showed a negative chronotropic action on Purkinje fibres while Morrow, Haley and Logic (1972) revealed a dose-dependent increase in the functional refractory period of the A–V conduction system. By increasing the atrial pacing rate using adrenaline or electrical stimulation, a critical rate was reached where arrhythmia was produced (Hashimoto and Hashimoto, 1972).

Similar studies by Atlee and Rusy (1972) indicated that halothane slowed conduction between the atria and the bundle of His and also slowed conduction in the ventricle. Atropine did not improve halothane-depressed conduction. When the electrophysiological effects of atropine were studied with recordings of the His bundle in humans, it was found that the drug shortened both the functional and effective periods of the A–V node, but appeared to have no direct effect on the His–Purkinje system. Aberrant ventricular conduction and block within the His–Purkinje system increased during premature atrial stimulation after the administration of atropine as a result of the shortening of the functional refractory period of the A–V node (Akhtar et al., 1974).

Hauswirth (1969) showed that halothane decreased conduction velocity as a result of increased internal resistance in the Purkinje fibres and this was not balanced by a shortening of the refractory period. Lesser effects were observed in ventricular fibres and the disparity between the two types of fibres could be a cause of arrhythmias.

In a recent study, Atlee and Rusy (1977) found that enflurane prolonged A–V nodal, but not His–Purkinje or ventricular conduction times, in contrast to their earlier studies with halothane, and they suggested that this may explain partly the clinical impression that ventricular arrhythmia appears less likely with enflurane.

The e.c.g. patterns of bundle branch block are attributed generally to a corresponding lesion in the bundle branches. However, another recent study suggests that asynchronous conduction within the His bundle itself, induced either by an altered refractoriness or by an anatomical lesion, may also result in similar e.c.g. patterns of partial or complete bundle branch block (Narula, 1977).

Rosenbaum, Elizari and Lazzari (1969) described a case of bi-directional tachycardia occurring in a diseased heart as a digitalis effect. When we consider the frequency with which these arrhythmias have been reported during anaesthesia in healthy patients with apparently normal hearts, undergoing all types of operation, but particularly exodontia, we conclude that they must be of a benign nature. Our clinical impression is that they occur more often in young patients, many of whom are athletic. However, in an analysis of 48 deaths which occurred during dental anaesthesia, Tomlin (1974) thought that perhaps as many as one-third were associated with circulatory disturbance. The findings of Hauswirth (1969) may explain, on the basis of re-entry in the ventricle itself, how ventricular fibrillation could occur, particularly in the presence of high plasma concentrations of catecholamines. Thus the presence of bi-directional tachycardia and fascicular block in patients undergoing surgery may be regarded, not as the mechanism for sudden cardiac death, but rather as indicating that suitable conditions may be present for this to occur. We have no reason to suppose that trifascicular (3rd degree) heart block might develop in our patients, or, if it did occur, that it would be more than transient (Rooney, Goldiner and Muss, 1976).

Our blood-gas studies did not reveal any difference between the various methods of induction of anaesthesia used, or the breathing system employed at the beginning of surgery. After approximately 1 h of surgery our blood-gas measurements supported the findings of Conway, Seeley and Barnes (1977) and indicate that the Bain system requires higher flows of fresh gas to prevent rebreathing, although with light anaesthesia the arterial carbon dioxide tension may be maintained at near normal values in spite of rebreathing carbon dioxide. We have confirmed recently the existence of rebreathing carbon dioxide (in the presence of normal Pa_{CO_2}) using a Capnograph Mark II (Gould Godart B.V.) carbon dioxide analyser. Gross hypercapnia was a feature in only one of the six patients who had conduction block and in whom blood-gases could be measured, and this case supports the relationship between increased concentrations of carbon dioxide and abnormal rhythms which is mediated presumably through increased circulating catecholamines (Wylie and Churchill-Davidson, 1972). In this patient the arrhythmia coincided with the onset of surgical stimulation. In studies to determine the "$P\text{CO}_2$ arrhythmia threshold" in the absence of surgical stimulation, Black (1967) found that Pa_{CO_2} values of 13.8 kPa or more were required before arrhythmia appeared during halothane anaesthesia.

During oral surgery, afferent impulses from the trigeminal nerve endings stimulate sympathetic nerve centres in the medulla and hence the cardiac sympathetic nerves in all subjects. In a small proportion of healthy patients a unique pattern of supraventricular tachycardia with conduction block was observed. The mechanism responsible for the supraventricular tachycardia is not clear. Experimental findings suggest that halothane should slow conduction at the atrioventricular node while atropine would have the reverse effect. Whatever the mechanism, the A–V junctional tissues exhibit increased automaticity, either by an ectopic pacemaker, or by a re-entry mechanism. The conducting fascicles in the His–Purkinje system are unable to respond to every beat, so that bundle–branch block patterns are produced. This is a physiological or pharmacological block and halothane must be partly responsible through its ability to decrease the speed of conduction in these fibres. We have no evidence to suppose that these patients have anatomically thinner fascicles than normal. Although supraventricular tachycardia is considered to be benign in the healthy heart, the disproportionate effect of halothane on conduction through ventricular muscle must make ventricular fibrillation a theoretical possibility at least, by micro re-entry in the ventricular wall. Carbon dioxide may play a role in the genesis of these arrhythmias in some patients, but others were normocarbic when arrhythmia occurred.

APPENDIX

The Cardiac Recorders 141 cathode-ray display unit is designed for use with one 142D isolated patient e.c.g. module, and up to four 152 Multi-range Pressure modules on channels 2–5. Switching channels were modified, 1, 2 and 3 to take e.c.g. and individually switched by a selector switch. This required moving channels 2, 3 and 4 pressure connections and replacing these with individual e.c.g. beam switch connections. The ultraviolet recorder was modified for trace shift facility (external mounting). Arterial pressure recording is possible, but not mentioned in the text.

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ARYTHMIE PENDANT LA CHIRURGIE DE LA BOUCHE: BLOCAGES FASCICULAIRES DANS LE SYSTEME CARDIAQUE CONDUCTEUR

RESUME

On a surveillé 204 malades pendant des interventions chirurgicales de la bouche, à l'aide de trois fils d'e.c.g. en surface utilisés simultanément. On a observé sur neuf malades une tachycardie supraventriculaire soutenue pendant la stimulation chirurgicale. Ce document traite du rôle de la stimulation sympathique et de l'anesthésie par l'halothane dans la production de l'arythmie.

ARRHYTMIE BEI ORALEN EINGRIFFEN. FASZIKULARE BLOCKIERUNGEN IM HERZLEITSYSTEM

ZUSAMMENFASSUNG

Zweihundertundvier Patienten wurden während oraler Eingriffe unter Verwendung dreier Elektrokardiogramm-Oberflachenleitungen überwacht, und zwar gleichzeitig. Bei neun Patienten wurde während der chirurgischen Stimulierung eine anhaltende supraventrikuläre Tachykardie beobachtet Die Rolle von sympathischer Stimulierung und von Halothan-Narkose beim Hervorrufen von Arrhytmie wird diskutiert.

ARRITMIA DURANTE CIRUGIA ORAL: BLOQUEOS FASCICULARES EN EL SISTEMA CONDUCTOR CARDIACO

SUMARIO

Se controlaron 204 pacientes durante cirugía oral, utilizando tres conductores superficiales de e.c.g. simultáneamente. En nueve pacientes se observó taquicardia supraventricular sostenida durante el estímulo quirúrgico. Se discute la función del estímulo simpático y anestesia de halotano en la producción de arritmia.

Br. J. Anaesth. (1979), **51**, 157

DOSE-RELATED TACHYCARDIA INDUCED BY PANCURONIUM DURING BALANCED ANAESTHESIA WITH AND WITHOUT DROPERIDOL

P. PARMENTIER AND P. DAGNELIE

SUMMARY

Pancuronium 0.02–0.08 mg kg^{-1} induced a dose-related increase of heart rate in patients anaesthetized with nitrous oxide supplemented with either fentanyl 0.003 mg kg^{-1} or fentanyl 0.003 mg kg^{-1} plus droperidol 0.15 mg kg^{-1}. The tachycardia was more marked following the administration of droperidol.

Pancuronium is known to cause tachycardia of variable degree in patients subjected to general anaesthesia (Foldes et al., 1971; Kelman and Kennedy, 1971; Stoelting, 1972; Grossman and McNeil Jacobi, 1974; Miller et al., 1975). Although it has been suggested that the degree of tachycardia may be related to the dose of pancuronium (Foldes, 1973) or to those other anaesthetic agents which have been administered concurrently (Takki and Tammisto, 1973), it is true that Miller and colleagues (1975) found no correlation between the degree of tachycardia and the dose of pancuronium. However, since it seemed to be of clinical interest to determine the relationship between the dose of pancuronium and the changes induced in heart rate, the effect of graded doses of pancuronium on the heart rate was studied in patients anaesthetized with nitrous oxide plus fentanyl, and with nitrous oxide supplemented with fentanyl and droperidol.

METHODS

The study was performed on 60 unselected adults of both sexes, free from gross cardiac disease and in sinus rhythm, who were to undergo elective surgery. Thirty minutes after the administration of diazepam 10 mg i.m., each patient received thiopentone 3.5 mg kg^{-1} followed by suxamethonium 1 mg kg^{-1}. The trachea was intubated and mechanical ventilation was instituted using a nitrous oxide in oxygen mixture (6 : 4). In half of the patients anaesthesia was supplemented with fentanyl 0.003 mg kg^{-1}. Fentanyl 0.003 mg kg^{-1} plus droperidol 0.15 mg kg^{-1} was given to the other 30 patients.

Both groups of patients were divided randomly into five subgroups of six. Five minutes after the induction of anaesthesia, subgroups 1 to 5 were given pancuronium 0.00 mg kg^{-1}, 0.02 mg kg^{-1}, 0.04 mg kg^{-1}, 0.06 mg kg^{-1} and 0.08 mg kg^{-1} respectively by injection. The heart rate was displayed on an electrocardioscope and recorded for 4 min immediately after the administration.

All observations were made before surgery and all patients were kept free from external stimulation. The minute volume of ventilation was determined using the Engström nomogram (Engström and Herzog, 1959). Commercially available drugs were used. Statistical analysis of the data included variance and covariance, and tests for linearity and parallelism (Dagnelie, 1973).

RESULTS

The control heart rates obtained in each subgroup are presented in table I. It was found that, following the administration of pancuronium, the heart rate was related linearly to the amount of drug administered (table II; fig. 1). In each subgroup, the slope of the line of best fit joining the corresponding group of means was highly significant ($P < 0.001$).

The prior administration of fentanyl plus droperidol was associated with greater mean heart rates when compared with the values obtained after fentanyl alone (as shown by a significant y-intercept difference at 2 and 3 min after pancuronium ($P < 0.05$)). Although the dose–response lines of pancuronium were consistently steeper after the fentanyl–droperidol

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TABLE I. *Control heart rates (beat min^{-1}) (mean ± SEM) for each subgroup of six patients, 5 min after the injection of fentanyl 0.003 mg kg^{-1} or fentanyl 0.003 mg kg^{-1} plus droperidol 0.15 mg kg^{-1}*

Subgroup	Fentanyl	Fentanyl and droperidol
1	70.3 ± 5.8	72.5 ± 2.5
2	74.3 ± 4.9	72.2 ± 8.4
3	68.3 ± 4.4	66.3 ± 2.7
4	67.7 ± 4.9	67.0 ± 2.0
5	73.5 ± 6.5	71.5 ± 2.6

mixture than after fentanyl alone, the differences were not significant.

Pancuronium did not cause cardiac arrhythmia in this study.

DISCUSSION

The mechanism by which pancuronium increases the heart rate is not yet clear, although it has been attributed to either an antimuscarinic (Saxena and Bonta 1971; Stovner, Oftedal and Holmboe, 1975) or a sympathomimetic effect (Ivankovich et al., 1975; Segarra Domenech, Garcia and Rodriguez Sasiain, 1976) of this drug.

Our data indicate that in patients receiving balanced anaesthesia, the heart rate changes induced by pancuronium are dose-related. Miller and colleagues (1975) observed no such correlation, but these authors used halothane and made observations during the operation.

The greatest variation in mean heart rate in our study represented a 15% increase from control, a value that agrees with the data of Stoelting (1972), but is less than the 25% increase reported by Kelman and Kennedy (1971). This difference may be attributable to the choice and dose of drugs. The interval between the administration of the other i.v. anaesthetic drugs and that of pancuronium was obviously important. The demonstration that fentanyl and droperidol exert their maximum effect within 5 min (Edmonds-Seal and Prys-Roberts, 1970; Price, 1975) justified our choice of a 5-min interval between the administration of either fentanyl or fentanyl–droperidol, and pancuronium. Yet it was evident from our results that the heart rates in those patients who did not receive pancuronium were unstable after 5 min. It is interesting that in the study by Kelman and Kennedy (1971), heart rate was still unstable 20 min after phenoperidine had been given. The 20-min delay may explain the stability of the tachycardia induced by pancuronium in their study compared with our patients who had a peak heart rate 1 min after pancuronium, followed by a gradual decrease during the

TABLE II. *Variations in mean heart rate (beat min^{-1} ± SEM) induced by pancuronium*

Time after injection of pancuronium	Subgroup: Pancuronium (mg kg^{-1})	1 0.00	2 0.02	3 0.04	4 0.06	5 0.08	$y = -a+bx$	b	Δa	Δb
1 min	fentanyl	−3.4	0.4	1.1	3.4	7.5	$y = -3.2+123x$	***		
		±0.6	±0.9	±2.5	±1.0	±2.9			n.s.	n.s.
	fentanyl + droperidol	−2.9	1.4	2.9	5.9	10.7	$y = -2.7+158x$	***		
		±0.8	±0.8	±1.7	±1.6	±3.5				
2 min	fentanyl	−4.4	−2.1	−0.6	2.7	5.5	$y = -4.6+122x$	***		
		±0.7	±1.0	±2.2	±0.6	±3.8			*	n.s.
	fentanyl + droperidol	−4.4	0.9	3.0	5.5	10.1	$y = -3.7+167x$	***		
		±0.4	±1.3	±1.6	±2.1	±3.3				
3 min	fentanyl	−5.5	−3.7	−2.7	2.2	5.7	$y = -6.4+141x$	***		
		±0.8	±1.3	±2.7	±0.6	±1.4			*	n.s.
	fentanyl + droperidol	−6.9	1.7	3.0	4.2	10.2	$y = -4.9+182x$	***		
		±0.5	±1.3	±1.9	±2.3	±3.2				
4 min	fentanyl	−6.7	−4.2	−3.2	1.9	4.9	$y = -7.3+145x$	***		
		±0.7	±1.3	±2.5	±0.7	±4.0			n.s.	n.s.
	fentanyl + droperidol	−7.2	−0.7	2.2	3.9	8.4	$y = -5.8+178x$	***		
		±0.7	±1.7	±2.0	±2.2	±3.8				

$y = -a+bx$ is the equation of the best fitting line joining the corresponding group of means. Δa, Δb: difference of a and b respectively between the fentanyl and the corresponding fentanyl–droperidol subgroups. ***$P < 0.001$ level of statistical significance; *$P < 0.05$ level of statistical significance.

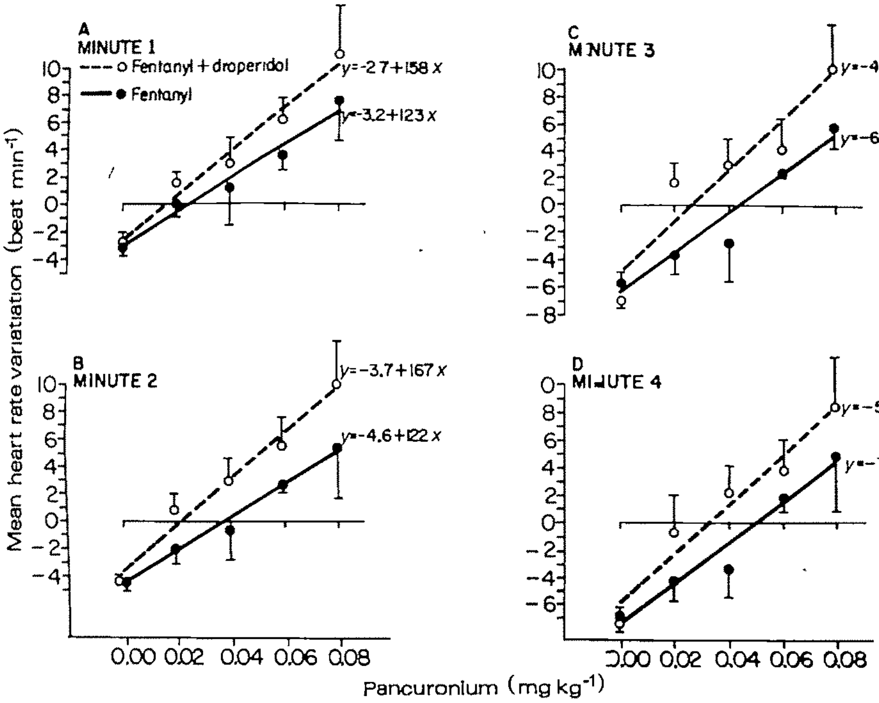

FIG. 1. Dose-response curve to pancuronium. Each data point represents the mean heart rate of 10 groups each of six patients, measured at 1, 2, 3 and 4 min after intravenous administration of the indicated dose of pancuronium.

next 3 min. Skin preparation and surgery precluded any further comparable observations.

The findings in the present study confirm the importance of the actions of other drugs on the changes in heart rate induced by pancuronium, as pointed out by Takki and Tammisto (1973). Pretreatment with fentanyl and droperidol produced a faster heart rate after the administration of pancuronium than with fentanyl alone. It is tempting to suggest that the alpha-adrenergic blocking properties of droperidol could be the explanation. Nevertheless, we found no differences in control heart rate between the subgroups receiving fentanyl and those receiving fentanyl and droperidol (table I). A similar observation was made by Stoelting and colleagues (1975). From our data we cannot determine the possible role of either an anti-muscarinic or a sympathomimetic effect of droperidol. Some authors deny that either haloperidol or droperidol has any anti-muscarinic properties (Janssen et al., 1963; Price, 1975; Niemegeers and Laduron, 1976), while others have suggested a very weak anti-muscarinic effect (Byck, 1975; Stanley, 1978).

In conclusion, our results show that the pancuronium-induced increase of heart rate and the dose of the drug are related, as has been suggested previously by Foldes (1973). The concurrent use of drugs such as droperidol might influence the degree of increase of heart rate.

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TACHYCARDIE EN FONCTION DE LA DOSE INDUITE PAR LE PANCURONIUM PENDANT UNE ANESTHESIE EQUILIBREE AVEC ET SANS DROPERIDOL

RESUME

La pancuronium, à raison de 0,02–0,08 mg kg^{-1}, a provoqué, en fonction de la dose, une augmentation du rythme cardiaque sur des patients anesthésiés au protoxyde d'azote additionné soit de fentanyl, à raison de 0,003 mg kg^{-1}, soit de fentanyl, à raison de 0,003 mg kg^{-1} plus dropéridol, à raison de 0,15 mg kg^{-1}. La tachycardie a été davantage marquée après l'administration de dropéridol.

DOSISABHÄNGIGE TACHYCARDIE, EINGELEITET DURCH PANCURONIUM, WÄHREND EINER AUSGEWOGENEN ANÄSTHESIE MIT UND OHNE DROPERIDOL

ZUSAMMENFASSUNG

Pancuronium 0,02–0,08 mg kg^{-1} leitete eine dosisabhängige Steigerung der Herzschläge in Patienten ein, die mit Lachgas anästhetisiert waren, das entweder mit Fentanyl 0,003 mg kg^{-1} oder mit Fentanyl 0,003 mg kg^{-1} plus Droperidol 0,15 mg kg^{-1} ergänzt worden war. Nach der Verabreichung von Droperidol trat die Tachycardie mehr hervor.

TAQUICARDIA INDUCIDA POR PANCURONIO RELACIONADA CON LA DOSIS DURANTE ANESTESIA EQUILIBRADA CON Y SIN DROPERIDOL

SUMARIO

El pancuronio 0,02–0,08 mg kg^{-1} indujo un aumento relacionado con la dosis de los latidos del corazón de pacientes anestesiados con óxido nitroso suplementado ya sea con fentanil 0,003 mg kg^{-1} o fentanil 0,003 mg kg^{-1} más droperidol 0,15 mg kg^{-1}. La taquicardia fue más acentuada tras la administración de droperidol.

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PREOPERATIVE STARVATION AND PLASMA GLUCOSE CONCENTRATIONS IN CHILDREN UNDERGOING OUTPATIENT ANAESTHESIA

I. F. M. GRAHAM

SUMMARY

Thirty-one children aged less than 5 years were studied while attending hospital for anaesthesia as outpatients. Plasma glucose concentrations were measured after the induction of anaesthesia. The mean plasma glucose concentration was 4.70 mmol $litre^{-1}$. No patient had a plasma glucose concentration less than 2.8 mmol $litre^{-1}$, despite at least 8 h of starvation. This is unexplained. It is suggested that the conclusions drawn from studies made in young inpatients may not be applicable to young outpatients.

As outpatient surgery becomes more popular, problems arise in the organization of anaesthesia. In paediatric practice it has been suggested that, in some patients, the period of starvation before operation may be excessive and may result in hypoglycaemia (Editorial, 1974). Preoperative feeding is sometimes employed in inpatient units, but this may not be practicable in outpatient units where a large number of patients may arrive simultaneously a short time before surgery.

At Alder Hey Children's Hospital, following studies made by Thomas (1974) which showed a surprisingly high frequency of hypoglycaemia in children of less than 4 yr, the feeding regime shown in table I is employed routinely for inpatients. However, it is considered unlikely that these instructions would be followed sufficiently closely by the parents of children admitted to the outpatient ward. Therefore, they are instructed that "your child should have nothing to eat or drink after midnight". This represents an attempt to minimize the frequency of regurgitation of stomach contents during the induction of anaesthesia. In order to investigate the effect of this instruction, a survey was made of the plasma glucose concentrations in outpatients.

TABLE I *Preoperative feeding of inpatients on the day of planned surgery*

(1) Infants less than 1 yr	
(a) Morning cases	No milk feed after midnight 5% dextrose 10 ml kg^{-1} at 6 a.m.
(b) Afternoon cases	Last milk feed at 7 a.m. 5% dextrose 10 ml kg^{-1} at 10 a.m.
(2) Children 1–5 yr	
(a) Morning cases	Milk 10 ml kg^{-1} at 6 a.m. (250 ml maximum)
(b) Afternoon cases	Light breakfast at 7 a.m. Milk 10 ml kg^{-1} at 10 a.m. (250 ml maximum)
(3) Children more than 5 yr	
(a) Morning cases	Nothing by mouth in the morning
(b) Afternoon cases	Light breakfast at 7 a.m.

METHODS

Over a 2-month period, patients less than 5 yr undergoing general anaesthesia on a morning operating list were studied. This age group was chosen following the observation (Thomas, 1974) that intraoperative hypoglycaemia was found only in children less than 47 months old. After explanation of the purpose and nature of the study to the parent accompanying the patient, verbal consent was obtained. Information about the time and nature of the last normal meal and the last feed or drink was collected. Patients less than 1 yr were premedicated with atropine alone, older patients received atropine 20 μg kg^{-1} and morphine 250 μg kg^{-1} 1 h before operation, except for one patient who received pethidine 1 mg kg^{-1} plus atropine, and four patients who received no premedication.

Anaesthesia was induced with thiopentone 4 mg kg^{-1}, which was followed by a neuromuscular blocking drug (tubocurarine 750 μg kg^{-1}, pancuronium

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$125\ \mu g\ kg^{-1}$ or suxamethonium $1\ mg\ kg^{-1}$). The trachea was intubated, and ventilation of the lungs with 66% nitrous oxide in oxygen was undertaken. Blood samples were withdrawn after the induction of anaesthesia but before surgery. Samples, either venous (28 patients) or capillary (three patients), were collected into fluoride bottles and sent to the laboratory for immediate analysis by the glucose oxidase method (Morley, Dawson and Marks, 1968).

RESULTS

Thirty-one patients were studied. The surgery performed consisted of herniotomy (11 patients), circumcision (eight patients), anal dilation (five patients), removal of skin nodule (two patients), removal of foreign body from head, division of tongue tie, avulsion of toenail, urethral dilation, sigmoidoscopy and polypectomy (one each). The age distribution of the patients is shown in figure 1. The mean plasma glucose concentration obtained after the induction of anaesthesia was 4.70 mmol $litre^{-1}$ (SEM 0.21 mmol $litre^{-1}$).

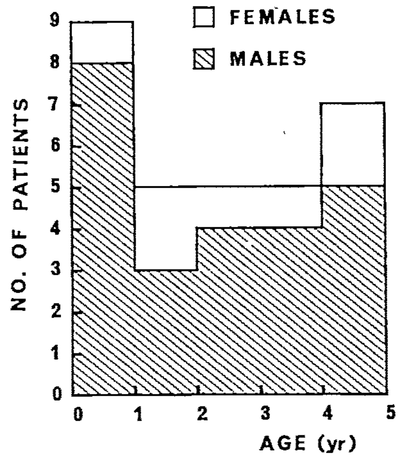

FIG. 1. Age distribution of patients studied.

The period of starvation before operation had ranged from less than 6 h to 17 h. There was no correlation between the duration of the period of starvation and the plasma glucose concentration (Spearman rank correlation coefficient = 0.07, $P > 0.5$) and this confirms an earlier study (Watson, 1972) which, however, included children up to 15 yr.

DISCUSSION

Hypoglycaemia has been defined variously as a blood glucose concentration of less than 2.2 (Cornblath and Schwartz, 1976), 2.8 (Ehrlich, 1971) and 3.3 mmol $litre^{-1}$ (Bowie, Mulligan and Schwartz, 1963) (40, 50 and 60 mg dl^{-1} respectively). Other studies of blood glucose concentrations obtained after the induction of anaesthesia (table II) have shown a frequency of hypoglycaemia which varied from 10% to 29% depending upon which definition was taken.

Caution must be exercised when comparing results from studies undertaken at different times and in different hospitals. The study reported by Thomas (1974) was undertaken in the same hospital as the present study and the plasma glucose concentration was measured by the same laboratory. The method of measuring the plasma glucose concentration had not changed, although results are expressed now in SI units (table III).

The patients studied by Thomas (1974) were in-patients who were anaesthetized using an anaesthetic technique similar to that employed in the present study, although pancuronium was the only neuromuscular blocking agent used. In addition, the patients had been premedicated with oral trimeprazine (Vallergan Forte) 3 h before operation, and blood was drawn from the long saphenous vein. The "starvation group" had received a light breakfast at 6 a.m., and were anaesthetized in the early afternoon.

TABLE II. *Frequency of hypoglycaemia after induction*

			No. of patients with blood glucose concn (mmol $litre^{-1}$)		
Study	Upper age limit	No. of patients	<2.2 (40 mg dl^{-1})	<2.8 (50 mg dl^{-1})	<3.3 (60 mg dl^{-1})
This study	5 yr	31	0	0	4 (13%)
This study	4 yr	24	0	0	2 (8%)
Thomas (1974)	47 months	18	5 (28%)		
Watson (1972)	15 yr	80	8 (10%)		
Bevan & Burn (1973)	10 yr	82			24 (29%)

TABLE III. *Comparison of blood glucose concentrations in patients immediately following the induction of anaesthesia. Maximum age in present study was 5 yr. (The same level of significance is found when patients less than 4 yr are compared with Thomas's studies*

	This study	Thomas (1974)
No. of patients	31	18
Mean blood glucose (mmol litre^{-1})	4.70	2.58
SD (mmol litre^{-1})	1.15	0.92
t		7.08
P		< 0.001

The present study concentrated on those patients considered by Thomas to be most at risk of developing hypoglycaemia. The apparent failure to demonstrate hypoglycaemia requires explanation. The possible relevance of different venous sampling sites is unknown. One would expect the glucose concentration in blood draining an exercising or recently exercised large muscle mass (for example, following a suxamethonium-induced fasciculation) to be less than in blood draining a more peripheral region. The influence of the different neuromuscular blocking agents has not been examined in this study.

Three of the plasma glucose concentrations were measured in capillary blood. If these three patients are excluded from consideration, the mean plasma glucose concentration is 4.59 mmol litre^{-1} while the standard error of the mean and the significance level of the difference from Thomas's study were unchanged. The use of an oral premedication containing sucrose 3 h before operation in Thomas's study may be relevant. However, as the maximum dose administered was equivalent to sucrose 3.25 g, it would seem unlikely to be the cause of a disturbance of plasma glucose concentration, particularly a rebound hypoglycaemia.

The present investigation, involving only 31 patients, does not indicate which of the factors are responsible for the apparent failure to demonstrate significant hypoglycaemia following the induction of anaesthesia. It may be that an extension of the long overnight fast is better tolerated than an extension of the fast between breakfast and luncheon. Prolonged starvation studies in children have been reported. Chaussain (1973) found that the capillary blood glucose concentration was significantly decreased after fasting for 8 h, while Chaussain and colleagues (1974) reported blood glucose concentrations which were decreased significantly after 24 h starvation.

Unlike the present study, these workers commenced the fasting period at noon. Bevan and Burn (1973), using arterialized capillary samples, studied a mixed group of inpatients, some of whom received an early breakfast, but all of whom had starved for at least 8 h. Of the 39 patients less than 5 yr, one appears to have had a blood glucose concentration of less than 2.8 mmol litre^{-1} (50 mg%). Whether the time of starting the fast affects the nature of the response to starvation in children remains unknown. Senior (1973) has pointed out that the tendency for young children to become hypoglycaemic during fasting may have been known in Biblical times, and suggested that research was needed into the biochemical differences between the adult and the young child's response to starvation.

The starvation period in these young patients is often very long, but the difficulty of formulating simple yet safe feeding instructions is formidable. (The problems of communicating with patients have been emphasized by Ley (1977).) The failure to demonstrate significant hypoglycaemia in this group of young outpatients has not been explained and requires further investigation.

Anaesthetists should be aware that young outpatients admitted and anaesthetized soon after admission represent a special category, and that studies made on inpatients may not be applicable.

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JEUN PREOPERATOIRE ET CONCENTRATIONS DE GLUCOSE DANS LE PLASMA CHEZ DES ENFANTS SUBISSANT UNE ANESTHESIE EN TANT QUE MALADES DE CONSULTATION EXTERNE

RESUME

Trente-et-un enfants âgés de moins de 5 ans ont été observés pendant qu'ils étaient à l'hôpital pour subir une anesthésie en tant que malades de consultation externe. Les concentrations de glucose dans le plasma ont été mesurées après l'induction de l'anesthésie. La concentration moyenne de glucose dans le plasma a été de 4,70 mmol litre^{-1}. Aucun des patients n'a eu une concentration de glucose dans le plasma inférieure à 2,80 mmol litre^{-1}, en dépit du fait qu'ils étaient tous à jeun depuis au moins 8 h. Ceci ne s'explique pas. On suggère que les conclusions tirées des études faites sur les jeunes malades hospitalisés ne sont pas applicables aux jeunes malades de consultation externe.

PRÄOPERATIVES FASTEN UND PLASMA-GLUKOSEKONZENTRATIONEN BEI KINDERN ALS AMBULANTE PATIENTEN NARKOTISIERT

ZUSAMMENFASSUNG

Einundreissig Kinder unter 5 Jahren wurden studiert, während sie als ambulante Patienten das Krankenhaus für Narkosezwecke besuchten. Die Plasma-Glukosekonzentrationen wurden nach Einleitung der Narkose gemessen. Der Mittelwert dafür betrug 4,70 mmol Liter^{-1}. Kein Patient zeigte Plasma-Glukosekonzentrationen von weniger als 2,8 mmol Liter^{-1}, trotz einem Fasten von mindestens 8 Stunden. Dies wird nicht erklärt. Man nimmt an, dass die aus Studien an jungen Krankenhauspatienten gezogenen Schlüsse nicht auf junge ambulante Patienten anwendbar sind.

AYUNO PREOPERATORIO Y CONCENTRACIONES DE GLUCOSA EN LA PLASMA DE NIÑOS SOMETIDOS A ANESTESIA DE CONSULTORIO

SUMARIO

Se estudiaron 31 niños de edad inferior a los 5 años mientras asistían al hospital para anestesia, en calidad de pacientes de consultorio. Se midieron las concentraciones de glucosa en su plasma después de la inducción de anestesia. La concentración media de glucosa en su plasma fue de 4,70 mmol litro^{-1}. Ninguno de los pacientes tuvo una concentración de glucosa en su plasma que fuera inferior a 2,8 mmol litro^{-1}, a pesar de un ayuno de por lo menos 8 h. Esto queda por resolverse. Se sugiere que las conclusiones formadas a base de los estudios de que fueron objeto los pequeños pacientes hospitalizados, probablemente no sean aplicables a los pequeños pacientes de consultorio.

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EFFECT OF HAEMOTHORAX ON PULMONARY ARTERY WEDGE PRESSURE

A case report

G. N. C. KENNY

SUMMARY

The pulmonary artery wedge pressure was increased because of the development of a haemothorax. After drainage of the haemothorax, the pulmonary artery wedge pressure was found to be less than that required to maintain an effective cardiac output and a rapid infusion of blood was required.

The value of flow-directed catheters to measure the pulmonary artery wedge pressure (PAWP) has become accepted increasingly in the monitoring of the critically ill patient (Forrester et al., 1971; Forrester, Diamond and Swan, 1972). In many conditions the central venous pressure is unreliable as an estimate of the circulatory capacity (Kelman, 1971; Buchbinder and Ganz, 1976), while the PAWP correlates well with the left atrial pressure and often provides a reliable guide to circulatory haemodynamics (Civetta and Gabel, 1972; Fitzpatrick, Hampson and Burgess, 1972). Many complications of the technique have been reported, and close control of its use has been recommended in an attempt to minimize these (Geha, Davis and Lappas, 1973; Zimmer and Maule, 1978).

This report describes a situation in which, at one point in the management of a patient, the PAWP gave an inaccurate indication of the circulatory capacity, and the critical condition of the patient was corrected only by disregarding the measurement.

CASE REPORT

A 63-yr-old man was admitted to the Respiratory Intensive Care Unit following Whipple's operation. Although his condition was satisfactory immediately after operation, the patient underwent further surgery for suspected intra-abdominal haemorrhage. On return to the intensive care unit he developed anuria with no response to diuretic therapy. An infusion of dopamine was commenced ($10\ \mu g\ kg^{-1}\ min^{-1}$), producing an increase in arterial pressure from 100/70 to 130/65 mm Hg and an increase in urinary output from 12 to 250 ml h^{-1} within 4 h.

Although the patient's lungs were being ventilated artificially, he required increasing concentrations of oxygen to maintain Pa_{O_2} satisfactorily. In addition, he developed a right-sided pleural effusion, aspiration of which resulted in a pneumothorax and a chest drain was inserted. In view of his continuing cardiorespiratory instability, a Swan–Ganz catheter was inserted and human plasma protein solution infused until PAWP was 18 mm Hg. Following the infusion, the arterial pressure increased from 110/75 mm Hg to the patient's pre-operative value of 160/95 mm Hg. However, since Pa_{O_2} was only 7.45 kPa (FI_{O_2} 1.0), positive end expiratory pressure (PEEP) was introduced and had to be increased gradually to 15 cm H_2O before an increase in Pa_{O_2} was obtained. Decreases in cardiac output subsequent to the increases in PEEP were minimized by adjustment of the rate of the infusion of dopamine. After 6 h PEEP was decreased gradually to 5 cm H_2O and FI_{O_2} reduced to 0.5, at which time Pa_{O_2} was 11.84 kPa.

The following day a chest x-ray showed the appearances of a subphrenic abscess and diagnostic aspiration was attempted. This produced only venous blood and the procedure was discontinued. The patient was observed closely for signs of blood loss, but his condition remained stable, with no blood loss from the chest or abdominal drains.

However, several hours later the patient suffered a further period of hypotension. Haemorrhage was suspected, but no evidence of blood loss could be detected. PAWP was found to be 22 mm Hg. In spite of this measurement, 100 ml of human plasma protein solution was infused rapidly whereupon

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PAWP increased to 26 mm Hg. Failure of the myocardium was suspected and the rate of dopamine infusion was increased to 30 μg kg^{-1} min^{-1}. However, there was no improvement in the patient's condition.

A chest x-ray, which had been taken shortly after the development of the last hypotensive episode, was now available and showed increased opacity of the right side of the chest. Since haemothorax seemed likely, two units of blood were infused rapidly and the position of the chest drain altered. Within a few minutes the systolic arterial pressure had been restored to 110 mm Hg, blood was obtained from the chest drain, and PAWP had decreased to 14 mm Hg. One hour after the infusion the cardiovascular system was stable with arterial pressure 130/50 mm Hg and PAWP 18 mm Hg.

DISCUSSION

Buchbinder and Ganz (1976) observed that the optimal point on the Starling ventricular function curve lies between PAWP of 15–18 mm Hg. Initially, following insertion of the Swan–Ganz catheter, fluid was infused until a PAWP of 18 mm Hg was achieved. This resulted in an increase in the patient's arterial pressure to its value before operation. In addition, the arterial hypoxaemia was improved greatly by the use of PEEP, although at one point 15 cm H_2O was required. The depressant effect of PEEP on the cardiac output was monitored by repeated measurements of the cardiac output and corrected by the use of dopamine, so ensuring adequate oxygen delivery to the tissues.

It would seem likely that the diagnostic aspiration for the suspected subphrenic abscess had punctured a blood vessel and resulted in the right haemothorax. Since the Swan–Ganz catheter tip had been positioned in the right pulmonary artery, PAWP had been affected by the development of haemothorax. Therefore, PAWP did not indicate accurately the left atrial pressure until the haemothorax had been drained. PAWP was then found to be less than that required by the patient to maintain a satisfactory cardiac output.

PAWP, while usually correlating closely with the left atrial pressure (LAP), underestimates LAP at pressures greater than 26 mm Hg (Lappas et al., 1973; Walston and Kendall, 1973). PAWP is also reported to underestimate LAP if more than 10 cm H_2O of PEEP is applied (Lozman et al., 1974; Qvist et al., 1975) but the degree of error must depend on the lung compliance and the amount of airway pressure transmitted to the mediastinum. If strict reliance had been placed on PAWP, it is likely that the patient would not have survived the episode, and this report underlines the fact that modern technology, while of great benefit in the majority of patients, can occasionally mislead the clinician.

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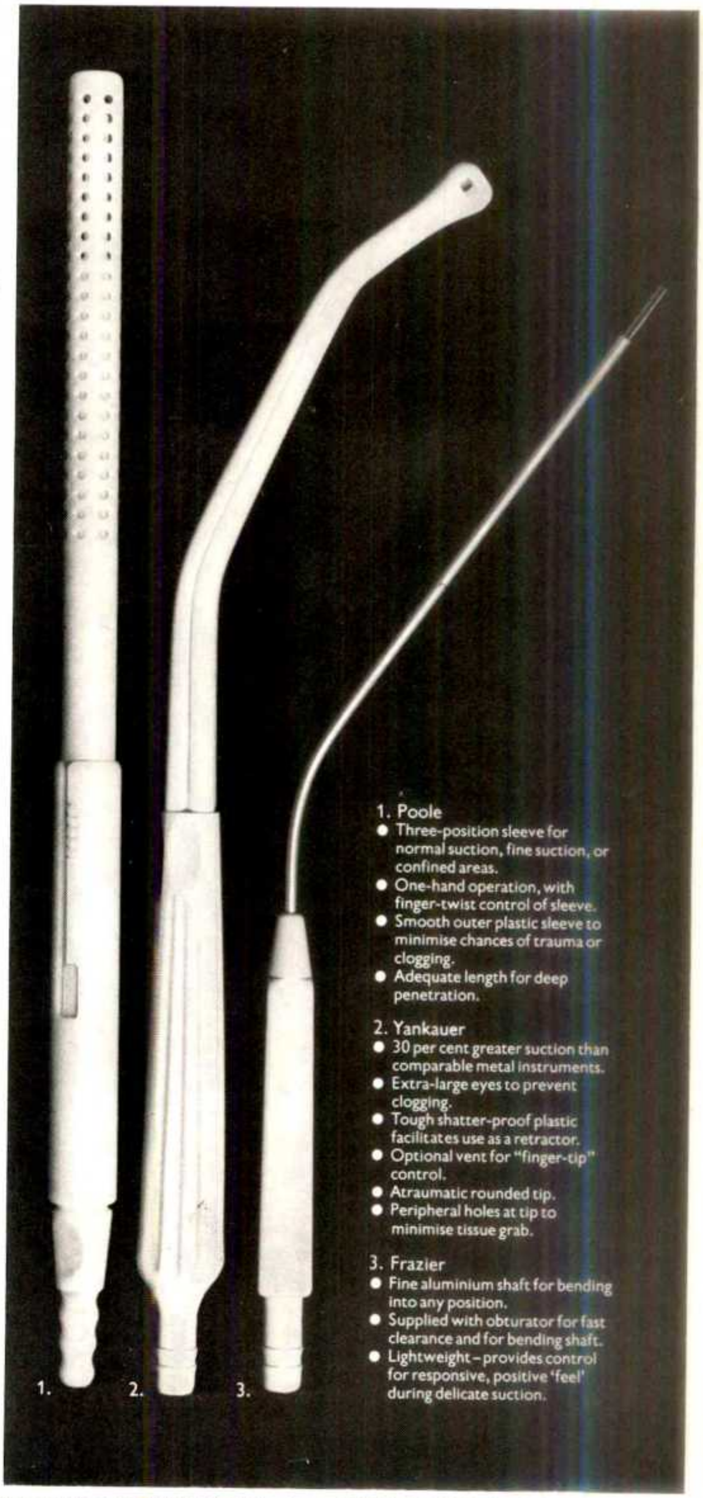

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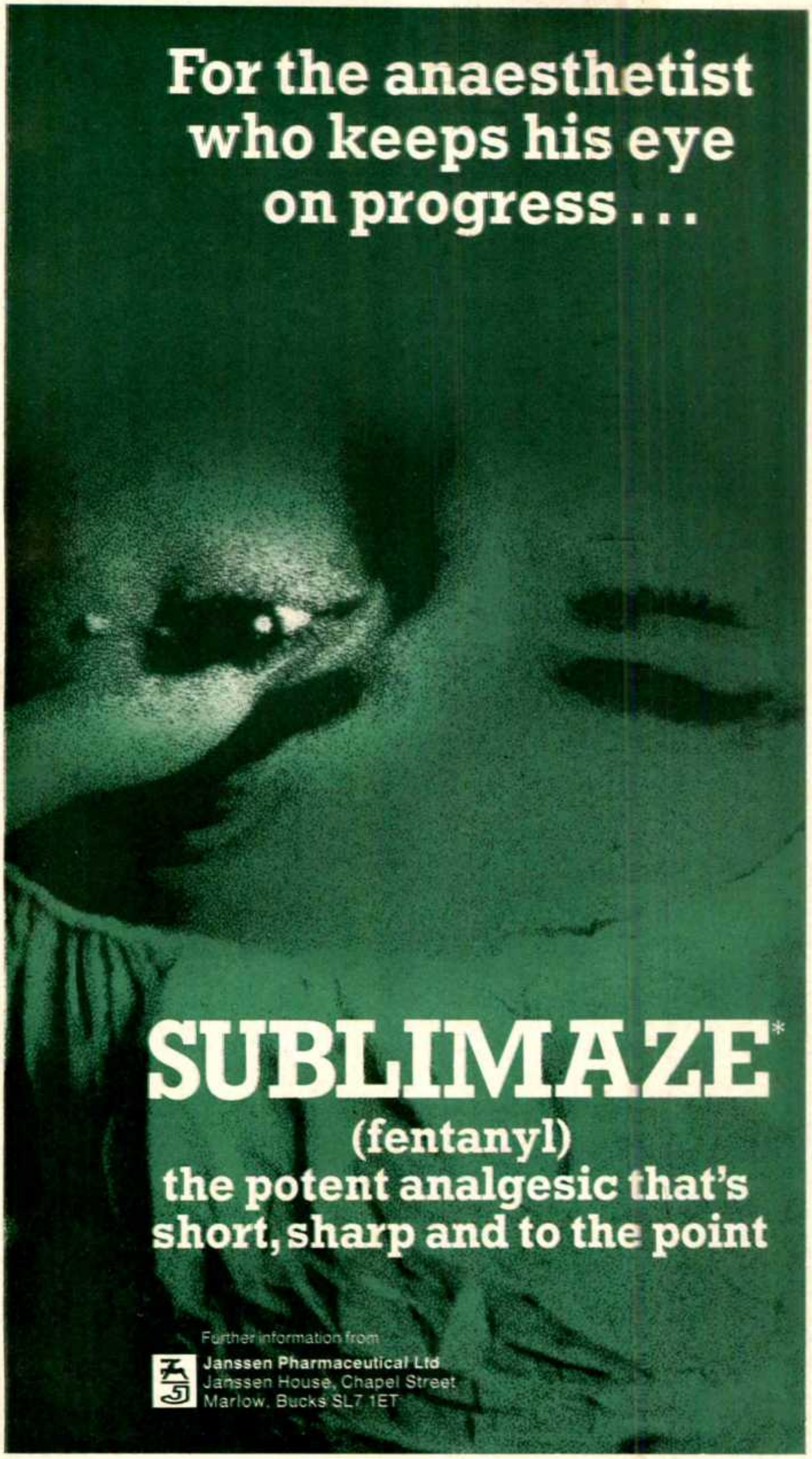
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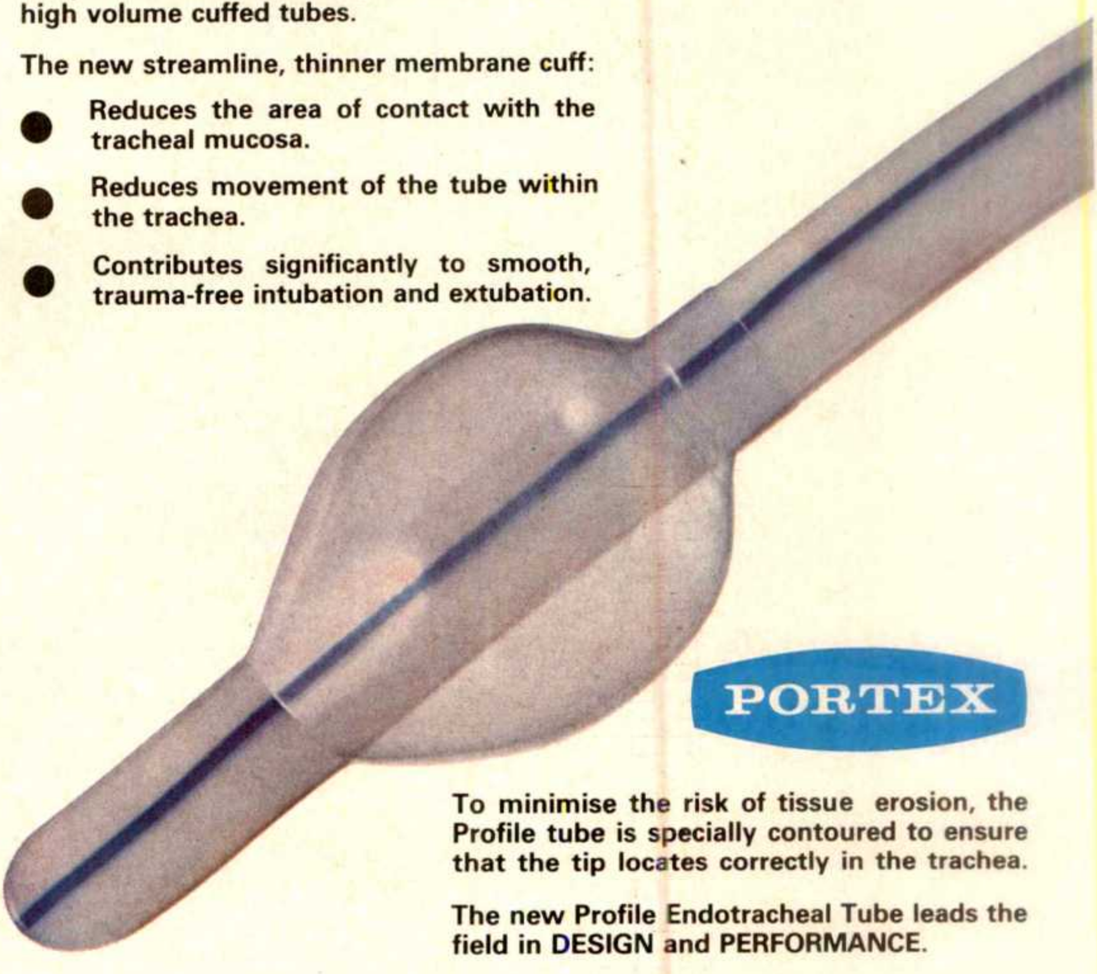

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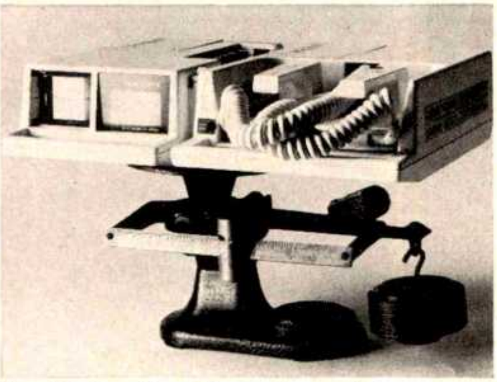

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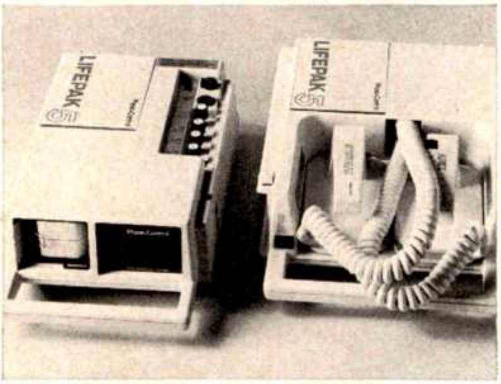

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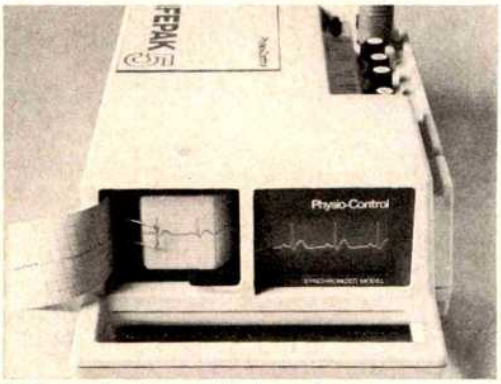

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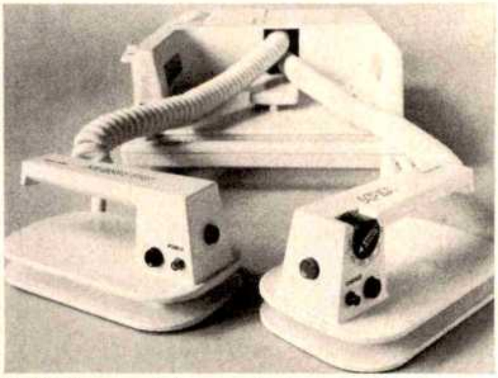

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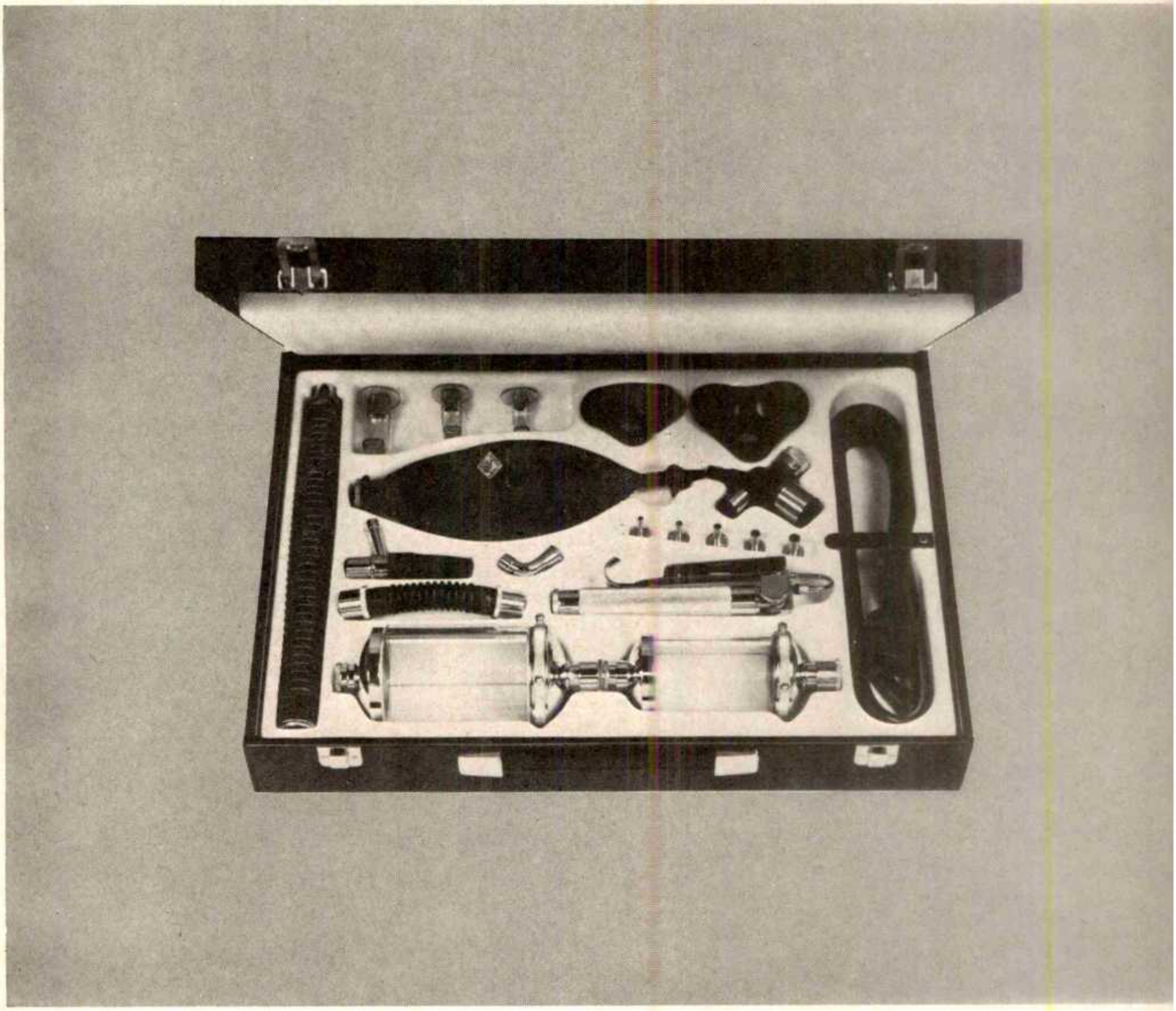

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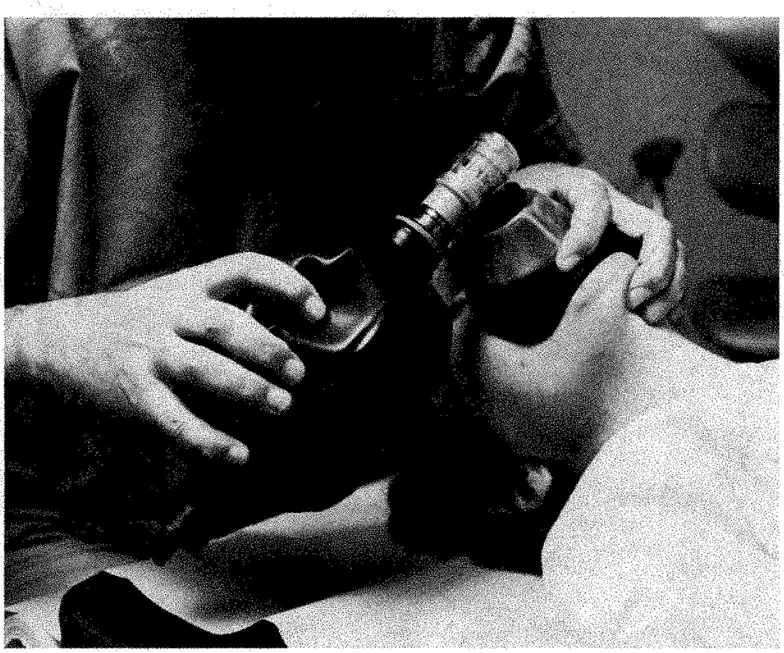

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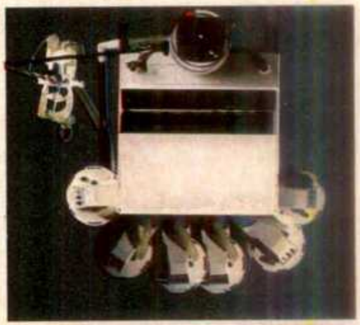

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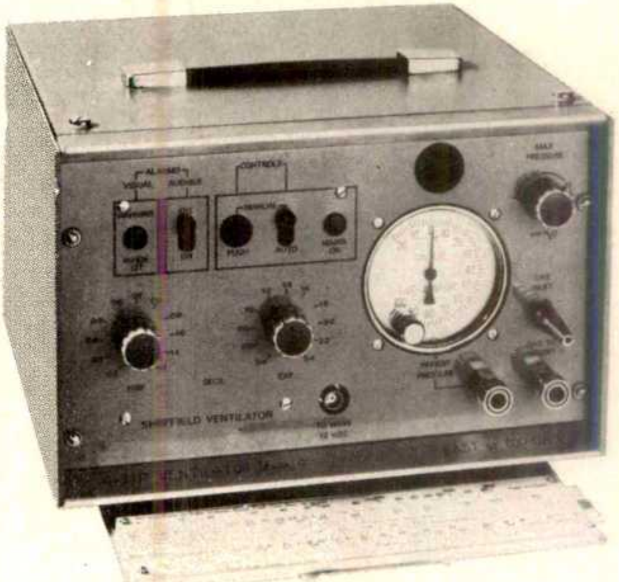

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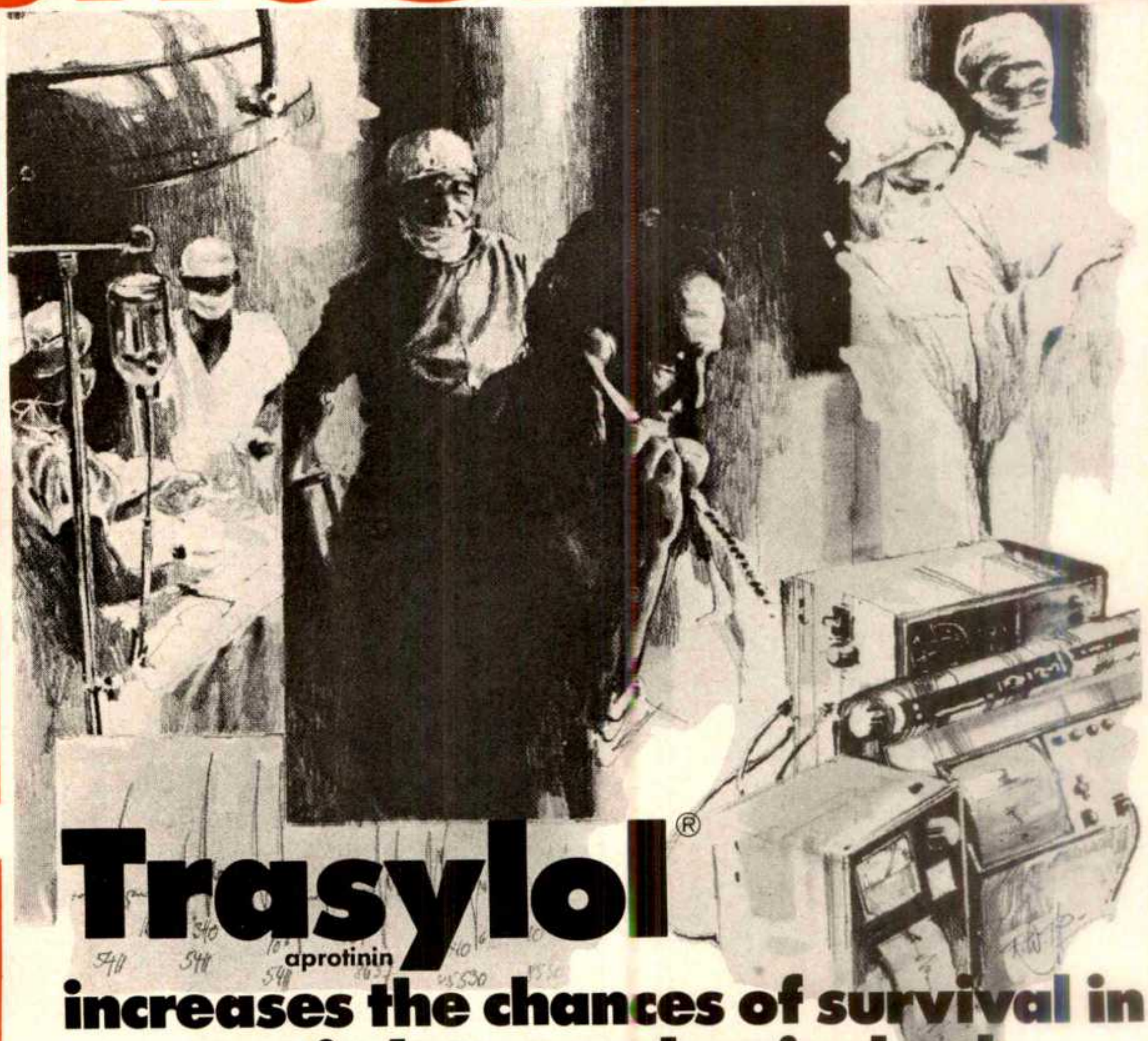

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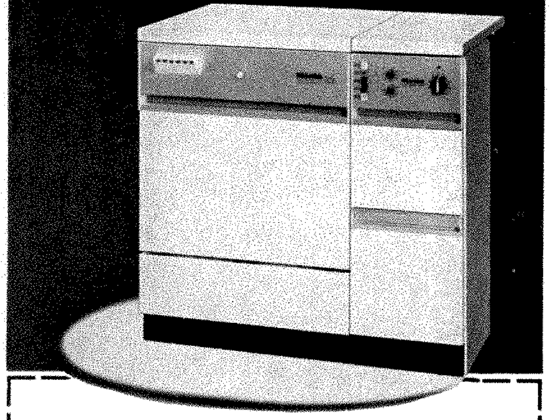

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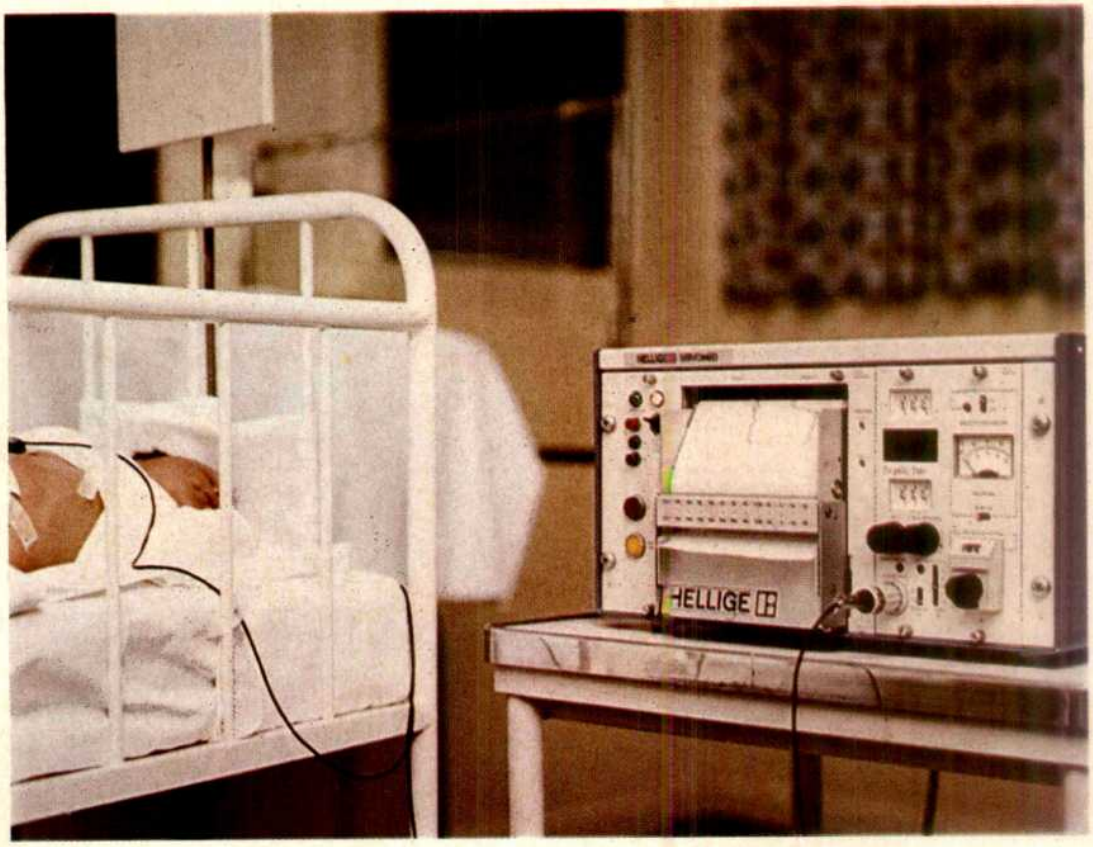

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BRITISH JOURNAL OF ANAESTHESIA

VOLUME 51, No. 3 MARCH 1979

EDITORIAL

MATERNITY SERVICES AND THE ANAESTHETIST

The full range of maternity services should be available to all mothers. Ideally, therefore, general anaesthesia must be readily available and there should be facilities for the effective relief of pain in labour, including the provision of a service for extradural analgesia. However, there are often strong local political pressures to preserve small maternity units and even to establish new units in situations where factors which have an important bearing on the wellbeing of the women who may be delivered there are disregarded.

There are a few obstetric emergencies, including prolapse of the cord, antepartum haemorrhage and some cases of acute fetal distress in labour, in which immediate delivery of the child offers the only chance of its survival. Forceps delivery, breech delivery and the delivery of twins may require urgent anaesthesia and the quality of that anaesthesia will influence the condition of the infant. Arguably, all obstetric anaesthetics are emergencies, if only because the risk of vomiting or regurgitation is high, and the minimum acceptable level of clinical competence requires at least one year's experience by the anaesthetist. It is therefore becoming the practice to have an anaesthetist, often of registrar grade, permanently on call to deal with obstetric emergencies and perhaps to provide extradural analgesia. In very large obstetric units there is the potential problem of two or more emergencies arising simultaneously. The largest units in the United Kingdom rarely have more than 4000 deliveries in a year and seem to manage with one registrar on call, with back-up from a senior registrar or consultant for difficult cases or multiple emergencies.

In the small maternity unit there is segregation of an experienced registrar anaesthetist who, although providing an important service, is sometimes underemployed, even though the training and expertise of an anaesthetist allows him to give valuable assistance in cases of haemorrhage, eclampsia, amniotic fluid embolism and many other conditions. In small units also, the anaesthetist regularly undertakes the resuscitation of the newborn infant. Despite these activities the resident anaesthetist in a small maternity unit may sometimes feel that his skills are not adequately exercised and a sense of frustration and resentment can grow. Yet the fact remains that obstetric units can only have the safe and satisfactory anaesthetic services they require by the exclusive allocation to them of an appropriately trained member of the junior staff.

The small maternity unit presents another problem. A District or Area with 1000 or fewer live births per year is likely to be small in all dimensions. A junior anaesthetic staff of perhaps one registrar and two senior house officers is by no means unlikely. Under such circumstances the allocation of a junior to the maternity unit can be made only at the expense of failing to meet all the demands which are made by other specialties on the services of anaesthetists.

The pattern of obstetric anaesthesia is changing. A growing number of women now receive lumbar extradural analgesia for the relief of pain in labour, for the delivery of twins and infants presenting by the breech, and as part of the management of pre-eclampsia and various medical conditions. The use of extradural and subarachnoid analgesia for Caesarean section is gaining favour. The result is that there is a much greater need for the presence of a consultant anaesthetist in the obstetric unit to teach techniques of regional analgesia to junior anaesthetists. In consequence an effective allocation of consultant sessions to the maternity unit is required also. Indeed, the Faculty of Anaesthetists insist on the designation of a named consultant in charge of the obstetric service as a condition of full recognition of a hospital or unit.

Overall it would seem that a unit with 2000 or more deliveries in a year can usefully and exclusively employ a member of the junior anaesthetic staff throughout each 24 hours and will justify the continuous presence of the anaesthetist within the maternity unit. Even with the obstetric extradural service, however, units with less than 1000 live births in a year are uneconomic in terms of anaesthetic manpower and may well be uneconomic in terms of other personnel and facilities; yet the wellbeing, and even the survival, of mother or child may depend on the ready availability of a full range of all services, including the services of a competent anaesthetist.

It is hoped that Health Authorities will consider this problem very seriously and adopt as a policy progressive centralization of maternity services and, where possible, close units with substantially fewer than 2000 deliveries a year, especially when these are isolated and under-used. The case for closure of the small maternity unit is doubly strong when it is separated by some miles from the related district hospital. Indeed, if the small maternity unit in a district general hospital is undesirable, and perhaps even unsafe because it has been impossible and simply uneconomic to provide the full range of services, then the isolated small unit is even more unsatisfactory.

It is hoped that when new maternity units are being provided they will be of appropriate size and built within or alongside an appropriate general hospital. It is particularly desirable that political pressures for the opening of small maternity units and splitting of larger ones should be resisted.

A. R. Hunter
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(*Br. J. Anaesth.*, **50**, 1232)

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Br. J. Anaesth. (1979), **51**, 171

IDENTIFICATION OF SUSCEPTIBILITY TO MALIGNANT HYPERPYREXIA IN SWINE

F. Okumura, B. D. Crocker and M. A. Denborough

SUMMARY

In vitro muscle contracture responses in swine susceptible to malignant hyperpyrexia (MH) were similar to those found in muscle from humans susceptible to this anaesthetic complication, confirming the suitability of the pig as an animal model for studying MH. The results suggest that there are different degrees of susceptibility to MH. Whichever drug was used, there was some overlap in the contracture responses between susceptible animals and controls, suggesting that the most accurate way of identifying susceptibility to MH is to use a variety of chemical agents, the best of which seem to be halothane, caffeine, suxamethonium and potassium chloride. Thymol, which is used as a preservative in commercial preparations of halothane, potentiates halothane contractures, but it is not known if this is significant clinically.

Individuals who are susceptible to malignant hyperpyrexia (MH) have an underlying disease of muscle. The most precise means of identifying susceptibility to MH is pharmacological testing *in vitro* on muscle from the individual in question.

Several different pharmacological tests are used. One examines the contracture response to caffeine (Kalow et al., 1970), another to halothane (Ellis et al., 1972), and a third studies the contracture response to a variety of agents including caffeine, halothane, suxamethonium and potassium chloride (Moulds and Denborough, 1974).

In the present study an attempt has been made to define the most reliable pharmacological tests for identifying susceptibility to MH, using susceptible swine as an animal model.

MATERIALS AND METHODS

Pure Landrace, pure Large White or crossbred Landrace–Large White swine were screened for susceptibility to MH using halothane anaesthesia. Anaesthesia was induced with 3% halothane in oxygen via a face mask, and maintained with 1–1.5% halothane. Rectal temperature was monitored continuously using a thermistor. MH was diagnosed by a rapid increase in temperature, stiffness of the legs, abnormal respiration and blotchy cyanosis of the skin. As soon as the diagnosis was made, the halothane was discontinued and the animal was cooled by sponging with water or alcohol. Tracheal intubation and artificial ventilation with pure oxygen was carried out and procaine hydrochloride 3–5 mg kg^{-1} and sodium bicarbonate were given i.v. if necessary.

All the control swine failed to develop abnormal symptoms or signs or an increase in temperature after halothane anaesthesia for 1 h followed by suxamethonium 2 mg kg^{-1} i.v. Nineteen of 326 swine were susceptible, of which 10 died during the challenge. One pig which died developed MH only after being given halothane and suxamethonium. The remainder developed the syndrome with halothane alone. The nine survivors consisted of five Landrace, three crossbred Landrace–Large White and one Large White.

The mean maximum body temperature during the challenge in the 19 susceptible swine was 40.2 ± 1.2 (SD) °C and the mean time to peak temperature from the beginning of halothane administration was 27.3 ± 14.3 min. The mean increase in temperature was 2.0 ± 1.0 °C.

Muscle biopsy and pharmacological testing

Muscle biopsy was performed in nine swine susceptible to MH and 16 control swine. Each pig was premedicated with ketamine hydrochloride 4–5 mg kg^{-1} i.m. and diazepam 0.5–1 mg kg^{-1} i.m. Tracheal intubation was performed after anaesthesia was induced with thiopentone 3–4 mg kg^{-1}. Anaesthesia was maintained with nitrous oxide in oxygen, supplemented with thiopentone.

F. Okumura,* M.D., PH.D.; B. D. Crocker, B.SC.; M. A. Denborough, M.D., D.PHIL., D.SC., F.R.C.P., F.R.A.C.P.; Department of Clinical Science, The John Curtin School of Medical Research, The Australian National University, Canberra, A.C.T., Australia.

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Biopsy specimens (4 cm long, 1 cm wide and 0.5 cm thick) were removed from the gracilis muscle after it had been clamped, and placed immediately in a muscle buffer at 37 °C bubbled with 5% carbon dioxide in oxygen (carbogen). The methods of preparing the muscle strips for pharmacological testing and for measurement of tension have been described previously (Moulds and Denborough, 1974). The maximum ischaemic time from excision of the muscle to the end of the experiment was 5 h. The initial resting tension for each preparation was 1 g. Before commencing the contracture experiments a single electric stimulus of 30 V was used to confirm the suitability of the muscle preparation. The stock solutions of the drugs used were caffeine 100 mmol litre^{-1} in muscle buffer, KCl 4 mol litre^{-1} in water, 5% suxamethonium chloride in water and thymol 50 mmol litre^{-1} in ethanol. Halothane was administered by passing carbogen through a calibrated Dragewick vaporizer.

Dose–response curves for each drug were obtained at 37 °C. For suxamethonium, potassium chloride and thymol, single bolus injections were used. For caffeine, successive doses were added as soon as the maximal contracture plateau induced by the previous dose of caffeine had been reached. Subsequently a dose was selected for each drug which appeared to give the maximal separation between susceptible and control swine, and the efficacy of the different drugs in identifying susceptibility to MH was compared.

Statistical analysis

Rigorous statistical analysis of the data was difficult, as there were large differences in the number of muscle preparations taken from individual pigs. One-way analysis of variance, of the type used for random effects and unequal sample size, was performed on the results from MH-susceptible pigs where the data allowed. The muscle preparations used for any particular drug test in the control group came from a large number of swine and there were few preparations from any individual pig. For this reason, the data were unsuitable for such an analysis, since the within-pig variance could not be estimated accurately. The variances for the tests in the control group result mainly from between-pig variability.

P values were obtained using Student's *t* test for unequal population variances, there being a greater variability in the MH-susceptible swine than in the control swine.

The methods used were those described by Snedecor and Cochran (1967).

RESULTS

The results of the analyses of variance are summarized in table I. Although variance ratios (*F* ratio) were not significant at either the 1 or 2.5% levels, they strongly suggest that heterogeneity exists in the MH-susceptible pig group, in that between-pig variability seemed larger than within-pig variability. Thus it was decided to estimate the components of variance and use these estimates to calculate the standard errors. In a single tension measurement the results show that, for the different drugs, between 77 and 88% results from within-pig differences and only 12–23% is associated with between-pig differences.

TABLE I. *Summary of one-way analysis of variance of drug-induced contraction in muscle from MH-susceptible swine*

Drug	Number of muscle preparations	Between animals		Within animals		Calculated *F* ratio	Tabulated *F* ratio (2.5% point)	Components of variance of a single measurement		Variance estimate of grand mean
		Mean square	d.f.*	Mean square	d.f.			Between animals	Within animals	
3% Halothane	58	0.45	7	0.22	50	2.0	2.6	0.032	0.222	0.008
Caffeine 2 mmol litre^{-1}	47	0.32	8	0.13	38	2.5	2.6	0.038	0.127	0.008
KCl 80 mmol litre^{-1}	34	1.40	8	0.92	25	1.5	2.8	0.133	0.922	0.047
Suxamethonium 1 mmol litre^{-1}	46	0.08	8	0.04	37	1.9	2.6	0.007	0.041	0.002
Thymol 100 μmol litre^{-1}	30	0.44	3	0.14	26	3.1	3.7	0.044	0.141	0.019

* Between-animal d.f. + 1 = number of animals.

Dose–response curves for caffeine, suxamethonium, potassium chloride and thymol are shown in figures 1–4.

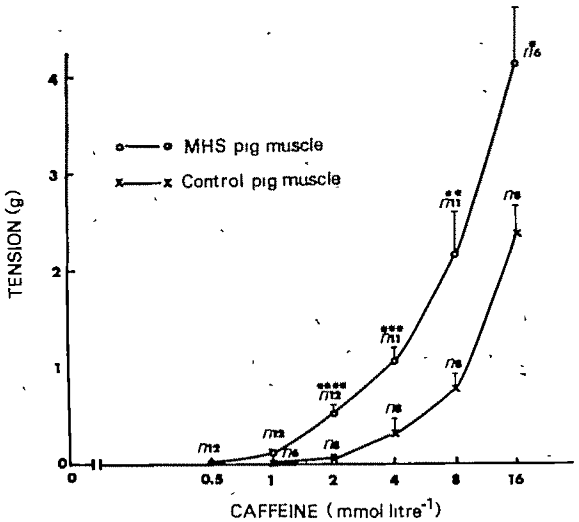

FIG. 1. Caffeine dose–response curves for contractures of gracilis muscle from swine susceptible to MH and from controls. The vertical bars represent SEM. *$P<0.05$; **$P<0.01$; ***$P<0.005$; ****$P<0.001$.

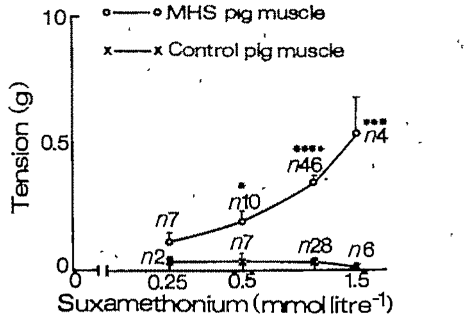

FIG. 2. Suxamethonium dose–response curves for contractures of gracilis muscle from swine susceptible to MH and from controls. *$P<0.05$; ***$P<0.005$; ****$P<0.001$.

Each of the drugs produced greater contractures in muscle from swine susceptible to MH than in controls. The mean concentration of caffeine required to increase the tension of muscle by 1 g was 4.6 ± (SEM) 0.7 mmol litre^{-1} in the swine susceptible to MH and 9.5 ± 0.7 mmol litre^{-1} in the controls ($P<0.001$).

Halothane induced contracture in muscle from susceptible swine at concentrations of 0.5%, 1% and 3%, but induced little or no contracture in the control muscle (fig. 5).

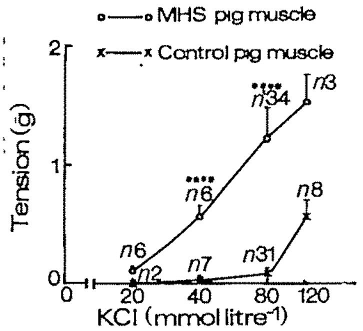

FIG. 3. Potassium chloride (KCl) dose–response curves for contractures of gracilis muscle from swine susceptible to MH and from controls. ****$P<0.001$.

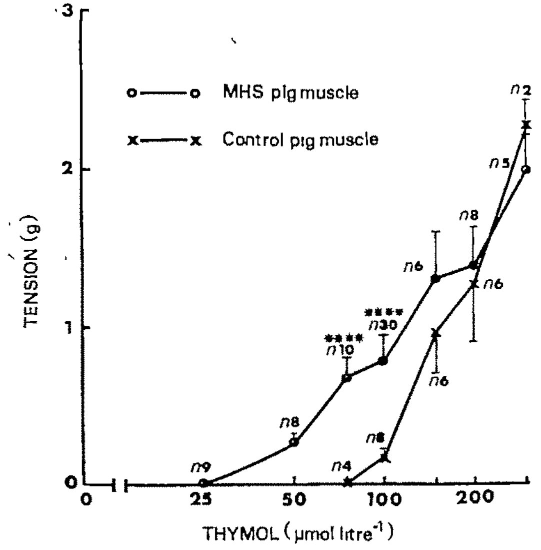

FIG. 4. Thymol dose–response curves for contractures of gracilis muscle from swine susceptible to MH and from controls. ****$P<0.001$.

The optimal concentration of each drug for separating susceptible from normal swine was decided by inspection of the dose–response curves. The concentrations selected were caffeine 2 mmol litre^{-1}, suxamethonium 1 mmol litre^{-1}, KCl 80 mmol litre^{-1}, thymol 100 µmol litre^{-1} and 3% halothane. Responses to these concentrations of the different drugs in swine susceptible to MH were compared with the responses in controls; the standard errors in the susceptible swine data being calculated from the components of variance as in Snedecor and Cochran (1967). The results are shown in table II and figure 6. The mean muscle contraction was significantly greater ($P<0.001$) in the susceptible swine than in the

TABLE II. *Drug-induced contraction in MH-susceptible swine (MHS) and in controls. The results expressed represent mean values* ±*SEM*

	MHS swine		Control swine		
Drug	Number of muscle preparations	Muscle contraction (g)	Number of muscle preparations	Muscle contraction (g)	P
3% Halothane	58	0.635 ± 0.09	26	0.005 ± 0.003	<0.001
Caffeine 2 mmol litre^{-1}	47	0.549 ± 0.09	32	0.032 ± 0.012	<0.001
KCl 80 mmol litre^{-1}	34	1.211 ± 0.23	31	0.084 ± 0.038	<0.001
Suxamethonium 1 mmol litre^{-1}	46	0.337 ± 0.04	28	0.024 ± 0.008	<0.001
Thymol 100 μmol litre^{-1}	30	0.757 ± 0.14	8	0.162 ± 0.059	<0.001

controls with each of the drugs (table II), but there was a wide scatter of results in susceptible swine with each of the drugs, and also some overlap in the results with the controls in each case (fig. 6).

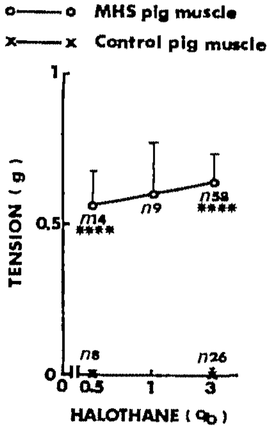

FIG. 5. Halothane dose–response curves for contractures of gracilis muscle from swine susceptible to MH and from controls. ****$P < 0.001$.

DISCUSSION

The *in vitro* behaviour of muscle from swine susceptible to MH was similar to that of muscle from humans who are susceptible to this anaesthetic complication (Moulds and Denborough, 1974). This confirms the usefulness of the pig as an animal model for studying MH.

The statistical analysis suggests that there is heterogeneity amongst MH swine in that between-pig variability seemed larger than within-pig variability. The between-pig differences are interesting and confirm clinical observations that the degree of susceptibility may differ both in humans and in swine.

In a single tension measurement on muscle from a randomly chosen MH-susceptible pig, the results show that between 77% and 88% of the variance for different drugs resulted from within-pig differences and only 12–23% was associated with between-pig differences. The within-pig differences reflect experimental factors which include a difference in the size of the muscle preparation, the temperature of the muscle bath and the ischaemic time from excision of the muscle to the end of the experiment.

Even when the maximum possible care is taken in the preparation and *in vitro* testing of muscle samples from both humans and swine, there is overlap in the amount of contracture induced by each of the agents currently used in identifying susceptibility to MH. This implies that the most accurate means of identifying susceptibility to MH is not to use a single predictive test, but to expose the muscle *in vitro* to a variety of chemical agents, the most efficient of which, at present, seem to be caffeine 2 mmol litre^{-1}, 3% halothane, suxamethonium 1 mmol litre^{-1} and KCl 80 mmol litre^{-1}.

Since thymol induces contracture of skeletal muscle (Ebashi, 1965) and because thymol is used as a preservative in commercial preparations of halothane, the effects of thymol on muscle were examined also in the present investigation. This seemed important as thymol appears to have a mode of action which is similar to but much more powerful than caffeine (Ogawa, 1970). With a low concentration of thymol (100 μmol litre^{-1}) the mean muscle contracture was greater in susceptible than in control swine, but there was more overlap with thymol than with the other drugs used. It is possible that a lower concentration of thymol (such as 75 μmol litre^{-1}) might identify susceptible muscle more precisely (fig. 4).

Although thymol is a potent inducer of skeletal muscle contracture, the contractures induced by

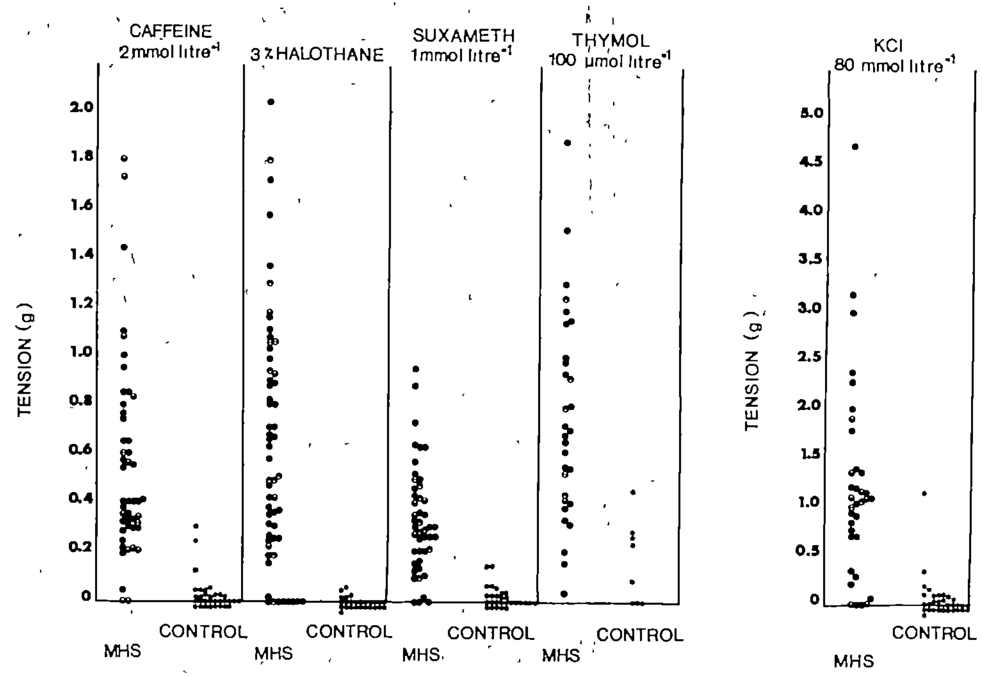

FIG. 6. Contractions induced by caffeine 2 mmol litre^{-1}, 3% halothane, suxamethonium 1 mmol litre^{-1}, thymol 100 µmol litre^{-1} and KCl 80 mmol litre^{-1} in MH-susceptible swine (MHS) and in controls. Each symbol represents the contraction induced in a single muscle preparation.

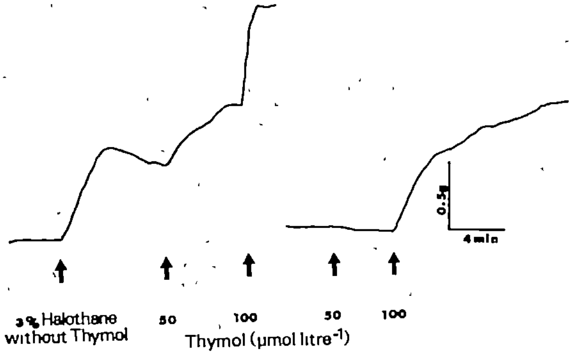

FIG. 7. Potentiation of thymol contracture by halothane in muscle from a pig susceptible to MH. The change in tension is shown on the vertical axis with time in minutes on the horizontal axis. Thymol 50 µmol litre^{-1} induced a contracture of 0.45 g in the presence of 3% halothane, but had no effect on its own.

halothane in muscle from swine susceptible to MH did not appear to be related to the presence of thymol as preservative. Special halothane preparations free from thymol also induced contracture in MH muscle. Halothane does potentiate the muscle contraction induced in susceptible swine muscle by thymol (fig. 7), and thymol potentiates halothane and potassium contractures (Okumura, Crocker and Denborough, 1978—unpublished observations), but it is not known if the thymol concentration in blood during halothane anaesthesia is sufficient to potentiate the halothane muscle contracture in an individual who is susceptible to MH.

ACKNOWLEDGEMENTS

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IDENTIFICATIONS DE LA SUSCEPTIBILITE A L'HYPERPYREXIE MALIGNE CHEZ LES PORCS

RESUME

Les réactions á la contracture du muscle *in vitro* ont été similaires, chez les porcs susceptibles à l'hyperpyréxie maligne (MH), à celles observées sur les muscles humains susceptibles à cette complication anesthésique, ce qui confirme que le porc convient comme animal type pour étudier la MH. Les résultats laissent penser qu'il y a différents degrés de susceptibilité à la MH. Quel que soit le médicament que l'on ait utilisé, il y a eu certains chevauchements dans les réactions à la contracture entre les animaux susceptibles et les animaux témoins, ce qui laisse penser que la méthode la plus précise d'identifier la susceptibilité à la MH est d'utiliser une variété d'agents chimiques, parmi lesquels les meilleurs semblent être l'halothane, la caféine, le suxaméthonium et le chlorure de potassium. Le thymol que l'on utilise comme agent de préservation dans les préparations commerciales d'halothane, peut entraîner les contractures par l'halothane, mais on ne sait pas si cela a une importance du point de vue clinique.

IDENTIFIZIERUNG DER ANFÄLLIGKEIT FÜR BÖSARTIGE HYPERPYREXIE IN SCHWEINEN

ZUSAMMENFASSUNG

Die Zusammenziehungsreflexe von Schweinemuskeln *in vitro* von Tieren die fur bösartige Hyperpyrexie anfällig waren ahnelten denen von Menschen, die fur diese Narkosekomplikation anfallig sind, damit wurde bestätigt, dass das Schwein als Versuchstier dienen kann, um bosartige Hyperpyrexie zu studieren. Die Resultate deuten an, dass es verschiedenen Grade der Anfälligkeit fur bosartige Hyperpyrexie gibt. Es kamzu einer Überschneidung der Ergebnisse der zusammenziehungsreflexe—ganz gleich, welche Droge angewendet wurde—zwischen den anfälligen Tieren und ihrer Kontrollgruppe, was darauf hinweist, dass die genaueste Methode zur Identifikation der Anfälligkeit auf bösartige Hyperpyrexie die ist, die eine Anzahl verschiedener chemischer Mittel benutzt. Die besten scheinen Halothan, Koffein, Suxamethonium und Kaliumchlorid zu sein. Thymol, das als Konservierungsmittel in Halothanpräparationen in Handel angewendet wird, verstärkt die Halothanzusammenziehungen, aber es ist nicht bekannt, ob dies klinisch von Bedeutung ist.

IDENTIFICACION DE SUSCEPTIBILIDAD A LA HIPERPIREXIA MALIGNA EN EL CERDO

SUMARIO

Las respuestas de contractura muscular *in vitro* fueron semejantes en los cerdos susceptibles a hiperpirexia maligna (MH) a las producidas en el músculo humano susceptible a esta complicación anestésica, confirmándose la conveniencia del cerdo como animal modelo para estudiar MH. Los resultados sugieren que hay diferentes grados de susceptibilidad a la MH. Con cualquiera de las drogas empleadas, se produjo cierta superposición de respuestas de contractura entre los animales susceptibles y los controles, lo que sugiere que la forma más precisa de identificar la susceptibilidad a la MH es el empleo de una variedad de agentes químicos, los mejores de los cuales parecen ser el halotano, cafeína, suxametonio y cloruro potásico. El timol, que se emplea como preservativo en preparaciones comerciales de halotano, da potencia a las contracturas de halotano, pero no se sabe si esto tiene significado clínico.

Br. J. Anaesth. (1979), **51**, 177

THRESHOLD CONCENTRATION OF NITROUS OXIDE AFFECTING PSYCHOMOTOR PERFORMANCE

R. H. Allison, A. W. Shirley and G. Smith

SUMMARY

Using audiovisual reaction times, no effects were found in 12 subjects exposed to 1, 2, 4, or 8% nitrous oxide. In subsequent studies on 30 subjects, a positive effect on performance was found at a concentration of between 8 and 12% nitrous oxide. In addition, there was no difference in mean reaction time in 12 subjects exposed to air or 8% nitrous oxide. It is concluded that the threshold concentration of nitrous oxide for an effect on psychomotor performance as assessed by choice reaction times probably lies between 8 and 12%.

Amongst the effects which have been attributed to contamination of the operating theatre with waste anaesthetic gases is impairment of the psychomotor and psychological performance of theatre staff. It is obvious that high subhypnotic concentrations of anaesthetics impair many aspects of performance, but it is important to determine if concentrations reached in both the unscavenged and scavenged operating theatre also cause a decrement in performance.

Previous studies from this department (Smith and Shirley, 1977) failed to confirm studies from Chicago indicating that concentrations of nitrous oxide of 500 p.p.m. with or without halothane 15 p.p.m. (Bruce, Bach and Arbit, 1974) affected psychomotor performance. Subsequently, the Chicago workers demonstrated a threshold concentration for nitrous oxide of between 25 and 50 p.p.m. (Bruce and Bach, 1976). A recent review (Smith and Shirley, 1978) of this subject stated that the balance of evidence indicated that much higher concentrations of nitrous oxide were required to affect psychomotor performance. We present additional evidence supporting this conclusion and also attempt to establish a threshold concentration.

METHODS

Twelve healthy subjects, age range 25–35 yr, gave informed consent to enter this study of the effect of four different concentrations of nitrous oxide on performance (1, 2, 4 and 8% nitrous oxide in air). All were anaesthetists or technicians and none was receiving any drug therapy at the time of this study. Each was requested to forgo tea or coffee during breakfast on the day of study and each was tested on two occasions at identical times of the same day of the week. After two practices with the audiovisual reaction-time equipment, the subject donned an Air Force type of mask and breathed air and measurements of reaction times were obtained. The gas was then changed to 1, 2, 4 or 8% nitrous oxide in air and after 1.5 h, reaction time measurements were again obtained. Subsequently, the inspired gas was changed to a different concentration of nitrous oxide and after 1.5 h, the measurements were repeated. On the second occasion, this procedure was repeated with the two concentrations of nitrous oxide not tested. The order of administration of the different concentrations of nitrous oxide was randomized and was not known to the subject. There were no significant differences between any of the measurements, but this pilot study suggested that an effect might be detectable with a concentration slightly greater than 8% and so this was tested.

Part 1

Thirty healthy subjects age 19–36 yr not receiving medication gave informed consent to enter this study. Apart from three technicians, all were junior anaesthetists in this department and there were three females. Each subject was tested on one occasion, but never on a day following a night of emergency duty. Each subject was allowed to sit comfortably and read magazines or journals during the course of the study.

Following two practice runs on the reaction time equipment, each subject donned an Air Force mask and breathed air. Reaction times were then obtained

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and the gas was changed to either 8 or 12% nitrous oxide, the order being randomized. After 1.5 h, audiovisual reaction times were measured. The gas was then changed to the concentration of nitrous oxide not tested initially and, after 1.5 h, the measurements were repeated.

Part II

As it was not possible to exclude a practice effect in the comparison of nitrous oxide and air in Part I, 8% nitrous oxide and air were tested in 12 subjects (aged 20–35 yr), all of whom were anaesthetists. The test sequence was similar to that of Part I in that subjects practised on the reaction-time equipment, donned the mask and breathed either air or 8% nitrous oxide for 1.5 h. Reaction time was then measured and the inspired gas changed to either 8% nitrous oxide or air, the order being randomized so that six subjects were exposed to air first and six to nitrous oxide first.

At no time during the experiments described in Part I or Part II was the mask removed or caffeine ingested. None of the subjects fell asleep during the course of the experiment and none was aware of the concentration of nitrous oxide in the gas delivered.

The audiovisual reaction-time test has been described fully in a previous communication (Smith and Shirley, 1977). The only difference in the reaction-time equipment as used in the present experiments was that the reaction times were counted electronically and recorded on an automatic printer, whereas previously reaction times were calculated manually from paper recordings. Nitrous oxide concentrations were obtained by dilution of Entonox with air (Smith and Shirley, 1977) and the concentrations delivered to the mask were monitored intermittently using a mass spectrometer (MGA 200). The concentrations were not found to vary outside the range of ±5% of the stated values. The means of about 90 measurements of correct reaction-time responses in each subject in each condition were used as the best estimate of the subject's reaction time in those conditions.

RESULTS

Part I

A "repeated" trial analysis of variance for the mean reaction times for the 30 subjects is shown in table I. Subsequent t tests on the treatment means using the error variance as the best estimate of the "population" variance from which to calculate the standard error of the difference between means showed that the only significant differences were those between the two pairs containing nitrous oxide ($P < 0.001$) (table II).

TABLE I. *Analysis of variance*

Source	Sum of squares	D.f.	Mean of squares	F ratio	P
Total	10.4502	89			
Subjects	8.2753	29	0.2854	8.947	<0.00001
Gas condition	0.3226	2	0.1613	5.0508	<0.001
Error	1.8523	58	0.0319		

TABLE II. *Mean reaction times for 30 subjects exposed to air, 8 and 12% nitrous oxide (SEM is standard error derived from error variance of the analysis of variance)*

	Air	8% N_2O	12% N_2O
Reaction time	1.2517	1.2787	1.3900
SEM	0.0374	0.0374	0.0374
		n.s.	$P<0.001$

As in our previous studies, the analysis also showed significant differences between subjects.

Part II

There was no significant difference in the mean reaction time for the 12 subjects during exposure to air or 8% nitrous oxide, as assessed by a paired Student's t test (table III).

TABLE III. *Mean reaction times for 12 subjects exposed to air or 8% nitrous oxide*

	Air	8% nitrous oxide
Mean	0.9520	0.9439
SEM	0.077	0.070
t		0.3475

DISCUSSION

Although previous studies from Chicago (Bruce, Bach and Arbit, 1974; Bruce and Bach, 1975, 1976) suggested that psychomotor performance was affected by concentrations of nitrous oxide as small as 25–50 p.p.m., three independent groups of workers failed to detect any measureable effects with 500 p.p.m. of nitrous oxide, using the same tests of performance (Smith and Shirley, 1977; Cook et al., 1978a; Frankhuizen et al., 1978).

There must, inevitably, be small differences in the design of experiments in four different laboratories, but one important difference in a previous study from our laboratory (Smith and Shirley, 1977) was that subjects were allowed to ingest caffeine during the course of the study. This factor has been excluded from the present study.

All the previous studies on this subject have been reviewed in detail recently by Smith and Shirley (1978), who concluded that small concentrations of nitrous oxide of the order of those encountered in unscavenged operating theatres (nitrous oxide 600 p.p.m. and halothane 10 p.p.m.) probably do not affect those aspects of performance which have been tested so far. This conclusion is supported by the results of the present study.

In addition, the results reported in Part I of this work suggest that the threshold concentration of nitrous oxide on those aspects of performance assessed by complex reaction times (Smith and Shirley, 1978) lies between 8 and 12%. In Part I, the exposure to air was not randomized, and the results with air were always obtained first during the experiment. Theoretically, therefore, one may postulate that 8% nitrous oxide may have a detrimental effect on performance which was counteracted by an effect of practice. Our experience with these tests suggests that after two practice routines of at least 200 manœuvres, there is little difference between two subsequent tests on air at an interval of 1.5 h. Nonetheless, to satisfy such an objection, we subsequently looked for an effect of 8% nitrous oxide on performance as described in Part II by a comparison of 8% nitrous oxide and air in a random, balanced sequence and found no effect (table III). We postulate, therefore, that the most reasonable conclusion to draw from these data is that the threshold concentration for nitrous oxide lies between 8 and 12%.

Confidence in these conclusions is strengthened by the close similarity between the results reported here and those obtained by Cook and others (1978a, b), who found that threshold concentrations for an effect of halothane, enflurane and nitrous oxide on performance (using an audiovisual reaction-time test very similar to that of Bruce, Bach and Arbit (1974)) were between 5 and 10% of the MAC value. Our data were obtained with anaesthetists and it is conceivable that they may be tolerant to trace concentrations of anaesthetics, but the fact that the data of Cook and colleagues were obtained with lay subjects renders such an objection unlikely.

We cannot account for the differences between our results and those of Bruce, Bach and Arbit (1974) and Bruce and Bach (1975, 1976), apart from suggesting that their subjects may have been influenced subliminally. However, the results of our study would appear to give further support to our belief (Smith and Shirley, 1978) that the balance of existing evidence (Smith and Shirley, 1977; Cook et al., 1978a, b; Frankhuizen et al., 1978) suggests that the concentrations of anaesthetic agents present in the atmosphere of unscavenged operating theatres do not affect psychomotor performance as assessed by the tests used in these studies.

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CONCENTRATION DE SEUIL DU PROTOXYDE D'AZOTE AFFECTANT LES PERFORMANCES PSYCHOMOTRICES

RESUME

En se basant sur les temps de réaction audiovisuels, on n'a décelé aucun effet sur les 12 sujets exposés à des concentrations de 1%, 2%, 4% ou 8% de protoxyde d'azote. Au cours d'autres études effectuées par la suite sur 30 autres sujets, on a trouvé un effet positif sur les performances lorsque les concentrations se sont situées entre 8% et 12% de protoxyde d'azote. De plus, il n'y a eu aucune différence dans le temps moyen de réaction sur les 12 sujets exposés à

l'air ou à 8% de protoxyde d'azote. On en a conclu que la concentration de seuil du protoxyde d'azote permettant d'obtenir un effet sur les performances psychomotrices, telles que déterminées par les temps de réaction choisis, se situe probablement entre 8% et 12%.

SCHWELLENKONZENTRATION VON STICKOXYD IN IHRER AUSWIRKUNG AUF DIE PSYCHOMOTORISCHE LEISTUNG

ZUSAMMENFASSUNG

Unter Verwendung audiovisueller Reaktionszeiten wurden keine Wirkungen bei 12 Patienten festgestellt, die 1%, 2%, 4% oder 8% Stickoxyd augesetzt wurden. Bei Untersuchungen an 30 weiteren Patienten wurde eine positive Wirkung auf die Leistung bei einer Konzentration von zwischen 8% und 12% Stickoxyd festgestellt. Daraus wird geschlossen, dass die Schwellenkonzentration von Stickoxyd fur eine Wirkung auf die psychomotorische Leistung, bewertet durch ausgewählte Reaktionszeiten, wahrscheinlich zwischen 8% und 12% liegt.

CONCENTRACION DE UMBRAL DE OXIDO NITROSO QUE AFECTA EL RENDIMIENTO SICOMOTOR

SUMARIO

Midiendo los tiempos de reacción audiovisual, no se observó efècto alguno en 12 sujetos expuestos a 1, 2, 4 o 8% de oxido nitroso. En estudios posteriores con 30 sujetos, se descubrió un efecto positivo sobre el rendimiento con una concentración de entre 8% y 12% de oxido nitroso. Además, no se produjo una diferencia en el período medio de reacción en 12 sujetos expuestos al aire o a 8% de oxido nitroso. Se concluye que la concentración de umbral de oxido nitroso que afecta el rendimiento sicomotor, según lo evaluado mediante los diversos tiempos de reacción, probablemente se encuentre entre el 8% y el 12%.

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IN VITRO INTERACTION OF PROPANIDID AND SUXAMETHONIUM WITH POOLED HUMAN PLASMA CHOLINESTERASE

A kinetic study

P. E. TAUSSIG, H. E. STOJAK AND N. R. BENNETT

SUMMARY

Human plasma cholinesterase (E.C. 3.1.1.8) was shown to be inhibited by physiological concentrations of propanidid and suxamethonium using a colourimetric assay at 25 °C and pH 7.2 unit with butyrylthiocholine as substrate. Propanidid inhibited the enzyme in a non-competitive manner ($I_{50} = 2.0$ mmol litre^{-1}; apparent $K_m = 6.6 \times 10^{-4}$ mol litre^{-1}) as did suxamethonium ($I_{50} =$ 4.4 mmol litre^{-1}; apparent $K_m = 1.6 \times 10^{-4}$ mol litre^{-1}). Combined inhibition produced K_m 3.0×10^{-3} mol litre^{-1}. The binding of these drugs to specific anionic sites in the vicinity of the active centre is thought to result in stereochemical changes in the enzyme. This mechanism and its relevance to the augmentation of the neuromuscular blockade produced by suxamethonium in the presence of propanidid is discussed.

There is evidence (Doenicke et al., 1968; Ellis, 1968; Kraunak, Pleuvry and Rees, 1977) which points to the involvement of a cholinesterase enzyme in the metabolism of the short-acting anaesthetic agent propanidid (propyl-4-NN-diethylcarbamoylmethoxy-3-methoxyphenylacetate). In human plasma the enzyme most likely to be involved in the hydrolysis of both propanidid and suxamethonium is pseudocholinesterase (E.C. 3.1.1.8) (Doenicke, Schmidinger and Krumey, 1968).

The loss of the anaesthetic potency of propanidid has been ascribed to cleaving of the n-propyl ester linkage (Doenicke et al., 1968), thereby producing an acid devoid of biological effect. *In vivo* studies have shown that propanidid prolonged the duration of action of suxamethonium (Doenicke et al., 1968) which itself acted as a substrate for plasma cholinesterase (Doenicke, Schmidinger and Krumey, 1968). In a recent study, Doenicke and others (1968) showed that the period of apnoea produced by suxamethonium was prolonged by more than 3 min in the presence of propanidid. This potentiation by suxamethonium has been the subject of a number of *in vitro* studies by Ellis (1968), Kraunak, Pleuvry and Rees (1977) and others who have sought to elucidate the nature of the interaction between propanidid, suxamethonium and neuromuscular blockade.

Ellis (1968), using a rat diaphragm preparation, showed elegantly that the duration of neuromuscular blockade produced by suxamethonium was potentiated by propanidid in a dose-related manner. It was shown also that this potentiation occurred in the presence of mipafox which completely inactivates cholinesterase at the neuromuscular junction. Thus it was postulated that propanidid could potentiate the effects of suxamethonium by a peripheral effect on the muscle cell membrane and that propanidid had little demonstrable anticholinesterase activity. In addition, propanidid could potentiate the neuromuscular blockade produced by tubocurarine.

Subsequent work has demonstrated that serum cholinesterase may be inhibited by pancuronium (Stovner, Oftedal and Holmboe, 1975) and ketamine (Schuh, 1975a). Stovner, Oftedal and Holmboe (1975) provided evidence that red cell acetycholinesterase was inhibited by pancuronium. The biological effect of pancuronium was potentiated by a number of i.v. agents in nerve-muscle preparations. The influence of ketamine on human plasma cholinesterase was studied by Schuh (1975a), who was able to show that the anaesthetic interacted in a non-competitive manner with the enzyme *in vitro*.

Despite the volume of data pertaining to the clinical evaluation of the potentiating effects of i.v. anaesthetic agents on the non-depolarizing myoneural blocking drugs, few attempts have been made to explore these interactions at the molecular level. Although the interaction between ketamine and pancuronium with human cholinesterases has been examined *in vitro* there has been no study of a combination of suxamethonium and propanidid.

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Plasma cholinesterase is important clinically when patients are exposed to myoneural blocking drugs and i.v. agents (Schuh, 1975b). In the present study the interactions between serum cholinesterase (E.C. 3.1.1.8), suxamethonium and propanidid were studied *in vitro*.

METHODS

Assay

The assay method was dependent on the ability of the enzyme butyrylcholinesterase to cleave butyrylthiocholine. Thiocholine, liberated in this reaction, reacts with 5,5′-dithiobis-2-nitrobenzoic acid which is present in a phosphate buffer solution to produce 5-mercapto-2-nitrobenzoate, which possesses a yellow colour. The change in optical density at 405 nm per unit time is a measure of butyrylcholinesterase activity, and was detected using a Beckmann DB GT spectrophotometer.

Butyrylthiocholine iodine and 5,5′-dithiobis-2-nitrobenzoic acid were obtained from British Drug Houses. Butyrylcholinesterase was obtained by pooling plasma from six healthy volunteers and storing it at −20 °C in 2-ml aliquots. Using a pipette, 3.0 ml of phosphate buffer (pH 7.20 unit) was introduced to the spectrophotometer cuvette followed by 0.1 ml of butyrylthiocholine solution. To this mixture was added 0.02 ml of plasma, the change in optical density was recorded using a Beckmann spectrophotometer and the results were displayed on a potentiometric chart recorder.

Suxamethonium and propanidid

The effects of separately varying concentrations of suxamethonium and propanidid on the reaction between butyrylthiocholine and butyrylcholinesterase were assessed. In addition, the effects of varying combinations of suxamethonium and propanidid in the reaction between substrate and enzyme were studied.

Dilutions of commercially available propanidid solubilized in 20% Cremophor EL (Bayer Pharmaceuticals) and suxamethonium (succinyldicholine, Burroughs-Wellcome Ltd) were made using distilled water.

Mathematical formulations

Fundamental Michaelis–Menten kinetics were applied to this enzyme:

$$\frac{V}{V_{\max}} = \frac{S}{K_m+S}$$

where

V = velocity of reaction at any substrate concentration S,

$V_{\max}$ = maximal attainable velocity when enzyme is saturated with substrate,

K_m = Michaelis–Menten constant.

Rates of reaction were measured in terms of the change in optical density per second and lines were plotted from the statistical calculations employing the method of least squares.

RESULTS

Human plasma cholinesterase was inhibited by propanidid in a concentration-dependent manner. The inhibitor (V_0/V_1 *v.* I) plot (fig. 1) for propanidid shows that the enzyme is 50% inhibited at a propanidid concentration of 2.0 mmol litre^{-1}.

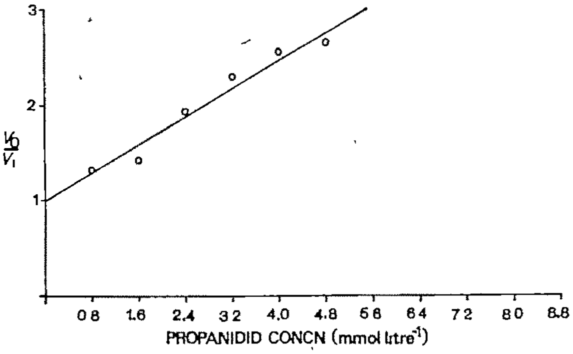

FIG. 1. Inhibitor (V_0/V_1 *v.* I) plot for human plasma cholinesterase with propanidid, where V_0 = rate of enzyme hydrolysis in the absence of any inhibitor and V_1 is the rate of hydrolysis in the presence of propanidid at each concentration of I. Propanidid concentration for half maximal inactivation at 2.0 mmol litre^{-1}.

The same plot for suxamethonium inhibition (fig. 2) yielded a value of suxamethonium 4.4 mmol litre^{-1} for half-maximal inactivation. The Lineweaver–Burk ($1/V$ *v.* $1/S$) plot for plasma cholinesterase in the absence of any inhibitor is shown in figure 3. The enzyme had K_m of 1.2×10^{-4} mol litre^{-1}.

The addition of 100 µlitre of undiluted propanidid to the buffer (corresponding to a molar concentration of anaesthetic in the cuvette of 4.04×10^{-3} mol litre^{-1}) inhibited the enzyme activity by more than 66%. Extrapolation of the line, produced by plotting the reciprocals of rate and substrate concentration

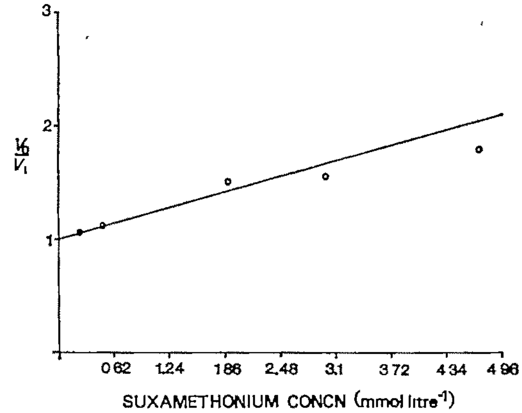

FIG. 2. Inhibitor (V_0/V_i *v*. *I*) plot for human plasma cholinesterase with suxamethonium. (See legend to figure 1 for explanation of symbols.) Suxamethonium concentration at half-maximal inactivation at 4.4 mmol litre^{-1}.

(fig. 3, a) for enzyme inhibited by propanidid, revealed that a 10-fold decrease in K_m had been produced by the addition of the anaesthetic agent. Exposure of the enzyme to 100-μlitre aliquots of propanidid diluted 50- and 200-fold with distilled water produced the same pronounced effect on K_m (fig. 3, b and c, and table I). In addition, the value of V_{max} at each concentration of propanidid which is shown by the intercept which each plot makes with the *y*-axis, was altered in all three instances. These data suggested that the interaction of propanidid with the enzyme was essentially of the non-competitive type.

Human plasma cholinesterase is shown to be inhibited by suxamethonium (figs 2 and 4, table I). K_m of the enzyme in the presence of suxamethonium

TABLE I. *Tabulated values of K_m and V_{max}/K_m for the enzyme in the presence of propanidid, suxamethonium and propanidid and suxamethonium, derived from Lineweaver–Burk and Eadie–Hofstee plots*

K_m (mol litre^{-1})	V_{max}/K_m	Inhibitor	Concentration (mol litre^{-1})
6.6×10^{-4}	3.2×10^3	Propanidid	4.04×10^{-3}
1.6×10^{-4}	12.5×10^3	Suxamethonium	12.4×10^{-3}
3.3×10^{-4}	6.0×10^3	Propanidid and suxamethonium	2.02×10^{-3} 6.2×10^{-3}
8.3×10^{-5}	2.4×10^4	Control—no inhibitor	—

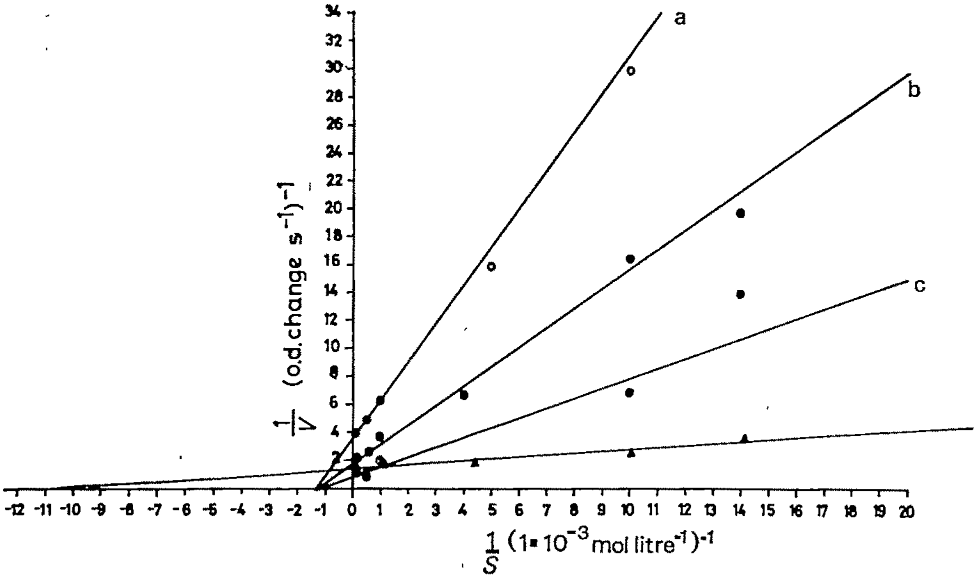

FIG. 3. Lineweaver–Burk ($1/V$ *v*. $1/S$) plot for human plasma cholinesterase in the absence of any inhibitor △. Values of K_m and V_{max} were obtained from the intercepts the line made with the *x*- and *y*-axes. (See text for explanation of symbols.) a, b and c: Lineweaver–Burk ($1/V$ *v*. $1/S$) plots for human plasma cholinesterase in the presence of propanidid. ○ = Propanidid 4.04×10^{-3} mol litre^{-1}; ● = propanidid 8.1×10^{-4} mol litre^{-1}; ⦶ = propanidid 2.2×10^{-4} mol litre^{-1}. Lines were plotted using the least squares method of regression analysis.

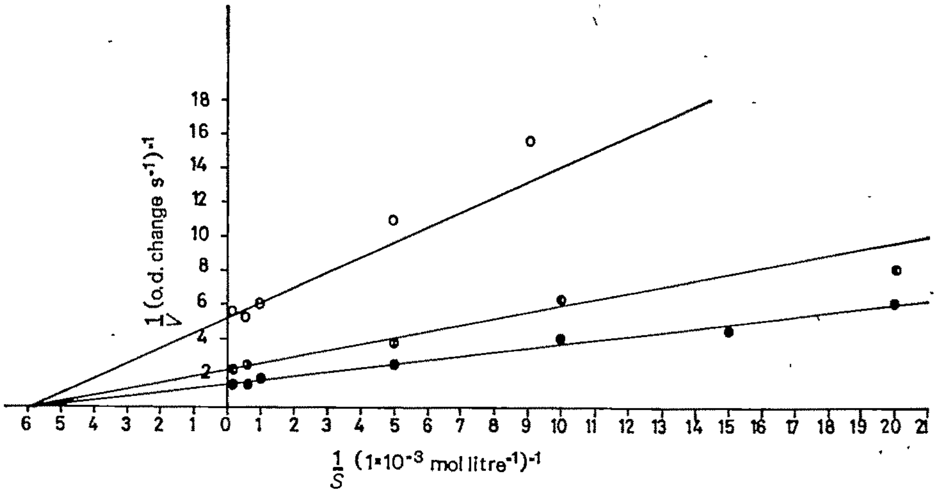

FIG. 4. Lineweaver–Burk (1/V v. 1/S) plot for human plasma cholinesterase in the presence of suxamethonium. ○ = Suxamethonium 12.4 mmol litre^{-1}; ⦶ = suxamethonium 0.49 mmol litre^{-1}; ● = suxamethonium 0.248 mmol litre^{-1}. Lines were plotted using the least squares method of linear regression analysis.

6.95×10^{-3} mol litre^{-1} is 1.6×10^{-4} mol litre^{-1}. Exposure of the enzyme to drug diluted 50- or 100-fold altered V_{max} but not K_m.

The effect on the enzyme of combining propanidid and suxamethonium is shown in table I. The anaesthetic and neuromuscular blocking drug mixed in a 1 : 1 ratio produced an apparent K_m 3.3×10^{-4} mol litre^{-1} which lay about half-way between the value of K_m produced by the action of propanidid and suxamethonium separately.

The tabulated intercepts resulting from Eadie–Hofstee (V v. V/S) plots of cholinesterase inhibition by propanidid, suxamethonium and a mixture of propanidid and suxamethonium are shown in table I. The value of V_{max}/K_m corresponded to the intercept which the line made with the x-axis.

DISCUSSION

From the data three conclusions may be drawn; (a) both propanidid and suxamethonium inhibit human plasma cholinesterase *in vitro*; (b) propanidid is the more potent inhibitor of the two; (c) the mechanism of inhibition is non-competitive in both instances.

In order to assess the clinical significance of these findings, it is necessary to correlate the *in vitro* concentrations of drugs used in the present study with those likely to be encountered in the blood in clinical practice.

An *in vitro* concentration of propanidid of 4.04×10^{-3} mol litre^{-1} produced a 66% inhibition of the enzyme under the conditions of the assay using the spectrophotometer. It was possible to detect inhibition of the enzyme at *in vitro* concentrations of propanidid as little as 2×10^{-5} mol litre^{-1}. These concentrations compare with the calculated *in vivo* values of 3.14×10^{-4} mol litre^{-1} assuming 0.5 g of propanidid to be distributed uniformly in 4 litre of plasma, or 8×10^{-5} mol litre^{-1}, which is equivalent to the concentration of the same dose of propanidid in 15 litre of extracellular fluid.

Inhibition of butyrylcholinesterase was observed at the *in vitro* concentration of suxamethonium of 10^{-5} mol litre^{-1}, which compares with the calculated *in vivo* values of 8.7×10^{-5} mol litre^{-1} and 2.31×10^{-5} mol litre^{-1} for blood and extracellular fluid respectively following a 100-mg bolus of suxamethonium.

However, these calculations are only estimates, and do not take into account factors such as protein-binding and ionization of the relevant drugs. It should be remembered also that the drug is exposed only to a finite quantity of enzyme in the spectrophotometer cuvette. *In vivo* the serum concentration of enzyme may exceed that of the cuvette by 150-fold. Attempts to demonstrate enzyme inhibition *in vivo* following the i.v. administration of 0.5 g of propanidid were unsuccessful (Alderson and Taussig, unpublished results, 1977). In contrast, Doenicke and others (1968) found that plasma cholinesterase activity was depressed by 20% following a similar exposure of the enzyme to propanidid in a normal volunteer. Clearly, individual differences exist in the ability to metabolize propanidid, but the high rate of clearance of this drug from the plasma by pseudocholinesterase and liver esterases makes the detection of *in vivo* inhibition a tenuous possibility.

We can only speculate as to the molecular mechanism underlying the potentiation of the action of suxamethonium by propanidid. The active centre of the cholinesterases contains two sites: an esteratic site and an anionic site (Bergmann, 1955). There are additional anionic sites around the periphery of the active site. Interactions of drugs bearing positively-charged moieties with these peripheral anionic sites may cause conformational changes in the active centre (Koshland, 1960, 1963). Conversely, conformational changes at the active centre may induce stereochemical changes in these anionic sites, making them less available for interactions with drugs bearing positively-charged groups, such as suxamethonium.

Therefore, prolongation of the action of suxamethonium by propanidid may be a result of the binding of propanidid to an anionic site, inducing a stereochemical distortion, trapping of the substrate in the active centre and either hindering the hydrolysis reaction or, possibly, the release of products from the active site. This would account for the predominantly non-competitive nature of the kinetics of the propanidid–cholinesterase interaction. The binding of suxamethonium, in the absence of propanidid, to a specific anionic site on the enzyme may cause a similar type of inhibition of function except that the degree of conformational change induced thereby would be less severe in view of the fact that suxamethonium is a less potent inhibitor of the enzyme than is propanidid. In the presence of both propanidid and suxamethonium the complex combination of stereochemical changes that results is sufficient to cause impairment of the binding of suxamethonium to the enzyme. In the clinical situation this would result in a greater proportion of the injected suxamethonium being made available at the neuromuscular junction with prolongation of suxamethonium action.

Mechanistic considerations apart, it may be concluded that plasma cholinesterase may be only partially responsible for the breakdown of suxamethonium and propanidid in man and that the interactions of these drugs with liver esterases and the cholinesterases of the neuromuscular junction may be the dominant mechanism.

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INTERACTION *IN VITRO* DU PROPANIDID ET DU SUXAMETHONIUM AVEC CHOLINESTERASE DU PLASMA HUMAIN MIS EN COMMUN

Etude cinétique

RESUME

Il a été démontré que la cholinestérase du plasma humain (E.C. 3.1.1.8) pouvait être inhibée par les concentrations physiologiques de propanidid et de suxaméthonium, en faisant une analyse colorimétrique à 25 °C et à un pH de 7,2, en utilisant comme substratum de la butyrylthiocholine. Le propanidid a inhibé l'enzyme d'une manière non compétitive ($I_{50} = 2$ mmol litre^{-1}; K_m apparent $= 6,6 \times 10^{-4}$ mmol litre^{-1}), tout comme le suxaméthonium ($I_{50} = 4,4$ mmol litre^{-1}; K_m apparent $= 1,6 \times 10^{-4}$ mmol litre^{-1}). L'inhibition combinée a donné un K_m de 3×10^{-5} mmol litre^{-1}. La liaison de ces médicaments su certains sites anioniques spécifiques à proximité du centre actif résulte, estime-t-on, des changements stéréochimiques de l'enzyme. On décrit dans cet article, ce mécanisme de même que son influence sur l'augmentation de blocage musculaire produit par le suxaméthonium en présence de propanidid.

IN VITRO WECHSELWIRKUNG VON PROPANIDID UND SUXAMETHONIUM MIT ANGESAMMELTER, MENSCHLICHER PLASMACHOLINESTERASE

Kinetische Untersuchung

ZUSAMMENFASSUNG

Durch eine kolorimetrische Analyse wurde gezeigt, dass menschliche Plasmacholinesterase (E.C. 3.1.1.8) durch physiologische Konzentrationen von Propanidid und Suxamethonium gehemmt wurde. Die Analyse wurde bei 25 °C und einer pH von 7,2 Einheiten Butyrylthiocholin als Substrat gemacht. Propanidid hemmte das Enzym in einer nichtkonkurrierenden Weise ($\text{Hemmer}_{50} = 2{,}0$ mmol liter^{-1}, sichtbare $K_m = 6{,}6 \times 10^{-4}$ mol liter^{-1}), und so auch Suxamethonium ($\text{Hemmer}_{50} = 4{,}4$ mmol liter^{-1}, sichtbare K_m $1{,}6 \times 10^{-4}$ mol liter^{-1}). Eine vereinte Hemmung produzierte eine K_m von $3{,}0 \times 10^{-3}$ mol liter^{-1}. Das Binden dieser Drogen an spezielle anionische Regionen in der Nähe des aktiven Zentrums, so denkt man, ergibt stereochemische Änderungen im Enzym. Dieser Mechanismus und seine Bedeutung auf die Verstärkung der neuromuskulären Blockade, die durch Suxamethonium im Beisein von Propanidid produziert wurde, wurde diskutiert.

INTERACCION *IN VITRO* DE PROPANIDIDA Y SUXAMETONIO CON COLINESTERASA REUNIDA DE PLASMA HUMANA

Un estudio cinético

SUMARIO

Se demostró que la colinesterasa (E.C. 3.1.1.8) en la plasma humana es inhibida por concentraciones fisiológicas de propanidida y suxametonio, empleando una prueba colorimétrica a 25 °C y una unidad de pH 7,2 con butiriltiocolina en calidad de substrato. La propanidida inhibió a la encima de forma no competitiva ($I_{50} = 2{,}0$ mmol litro^{-1}; K_m aparente $= 6{,}6 \times 10^{-4}$ mol litro^{-1}), así como lo hizo el suxametonio ($I_{50} = 4{,}4$ mmol litro^{-1}; K_m aparente $= 1{,}6 \times 10^{-4}$ mol litro^{-1}). La inhibición combinada produjo un K_m de $3{,}0 \times 10^{-3}$ mol litro^{-1}. Se piensa que la unión de estas drogas a determinados sitios aniónicos próximos al centro activo, da por resultado cambios estereoquímicos en la encima. Se discute este mecanismo y su relevancia al acrecentamiento del bloqueo neuromuscular producido por suxametonio en presencia de propanidida.

Br. J. Anaesth. (1979), **51**, 187

FAILURE OF CLINICAL CONCENTRATIONS OF HALOTHANE TO BLOCK ADENOSINE DIPHOSPHATE-INDUCED PLATELET AGGREGATION *IN VITRO*

D. G. BJORAKER

SUMMARY

A dose-related inhibition by halothane of adenosine diphosphate-induced platelet aggregation was measured for human platelets in plasma anticoagulated with sodium citrate 6.8 mmol litre^{-1} or 13.6 mmol litre^{-1}, or heparin 2 u. ml^{-1} and for platelets separated from plasma by albumin density gradient centrifugation and requiring no anticoagulant. By maintaining exposure and assay temperature at 37 °C, maintaining physiological pH, avoiding age-related deterioration and using an atraumatic equilibration method, no inhibition was found at clinical concentrations of halothane and 50% inhibition required greater than halothane 10%. Sodium citrate, a calcium chelating anticoagulant, was found to enhance halothane inhibition.

Extensive interest in the clinical implications of platelet dysfunction has led to efforts to define the causes of acquired dysfunction. Since other inhibitors of platelet aggregation such as aspirin may enhance haemorrhage (Sutor, Bowie and Owen, 1971), the question of whether anaesthetic agents increase haemorrhage during operation by this method has been raised. Volatile general anaesthetics have been reported to be inhibitors of platelet aggregation induced by adenosine diphosphate (ADP) (Ueda, 1971).

In order for haemostasis to occur, it is necessary for a platelet–fibrin plug to form at the site of the vascular leak. Platelets must adhere to the damaged vessel, aggregate and release endogenous substances which cause further aggregation and release. ADP, an important inducer of *in vivo* aggregation when added to platelet-rich plasma (PRP) *in vitro* will cause primary aggregation and, in sufficient concentration, the release of endogenous platelet ADP.

When platelets, suspended in plasma *in vitro*, are induced to aggregate, the light transmission of the plasma increases (Born, 1962; O'Brien, 1962). Since this change in transmission may be displayed graphically and used to quantitate aggregation, prior exposure to drugs will indicate the effect of the drug on this aspect of platelet function. However, the volatility of halothane and the plasma handling necessary prohibit the study of *in vivo* exposure by subsequent *in vitro* assay. Exposure must also be *in vitro* if one is to be assured that the platelets being studied are still equilibrated with a known amount of anaesthetic.

Ueda (1971) has reported a dose-related suppression of ADP-induced platelet aggregation with aggregation inhibited by 50% at 1.0 kPa partial pressure of halothane. Since, clinically, there is an apparent absence of enhanced bleeding during halothane anaesthesia, this investigation reconsidered the effects of halothane on platelet aggregation with several experimental modifications. (1) Human, not canine, platelets were used. (2) All assay and anaesthetic exposure temperatures were at 37 °C. (3) Since plasma equilibrated with room air rapidly becomes alkalotic (pH usually greater than 8.0), pH was maintained in the physiological range. (4) To avoid deterioration with time, the study of all platelet suspensions was complete within 3.5 h of venepuncture. (5) The reversibility of the effect of halothane was investigated to assure the method of study alone did not result in diminished aggregation. (6) Equilibrium with the anaesthetic agent was verified. (7) The effect of calcium chelating anticoagulants was investigated also, by studying PRP with two concentrations of citrate, heparinized PRP and platelets separated from plasma by albumin density gradient centrifugation.

METHODS

Whole blood was obtained by venepuncture, using a two-syringe technique, from healthy male volunteers with no history of recent drug exposure. Nine parts blood were immediately mixed with one part anticoagulant solution: sodium citrate 68 mmol litre^{-1} or 136 mmol litre^{-1} or porcine heparin 20 u. ml^{-1} in

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isotonic saline, for the three preparations studied directly. PRP was prepared by centrifugation of whole blood for 12 min at 250 *g*. The platelet count was adjusted to 200 000 μl^{-1} by addition of platelet free plasma (PFP) prepared by 15 min centrifugation at 2200 *g*. Plasma was maintained for no longer than 3.5 h in a 5% carbon dioxide in air atmosphere at 37 °C to preserve physiological pH (Han and Ardlie, 1974). Plastic or siliconized glassware was used throughout the experiment.

The fourth preparation of platelets studied was made free of procoagulants and therefore did not require an anticoagulant. It was prepared by modification of the albumin density gradient technique of Walsh, Mills and White (1977). Following preparation of PRP with sodium citrate 12.9 mmol litre^{-1}, 7–8 ml was layered over a 2-ml gradient of bovine serum albumin (BSA) (Sigma Chemical, fraction V) buffered with NaOH 2 mol litre^{-1} to pH 7.40 at 37 °C. The discontinuous gradient was composed of four 0.5-ml aliquots of approximately 40, 27, 20 and 16 g dl^{-1} BSA respectively. Following 15 min centrifugation at 1200 *g* the lower 2.5 ml was resuspended in 5.5 ml of an isotonic electrolyte solution buffered to pH 7.40 at 37 °C. The solution composition was glucose 5.55 mmol litre^{-1}, NaCl 140 mmol litre^{-1}, KCl 5.4 mmol litre^{-1}, $MgCl_2.6H_2O$ 1.0 mmol litre^{-1}, Tris–HCl 10.5 mmol litre^{-1} and Tris base 4.0 mmol litre^{-1}. The resulting suspension was relayered twice over a BSA gradient and centrifuged at 1000 *g* for 15 min. The resulting suspension was adjusted to a platelet count of 200 000 μl^{-1} and $CaCl_2$ 100 mmol litre^{-1} was added to achieve an ionized calcium concentration of approximately 1.0 mmol litre^{-1} as measured by an Orion model SS-20 calcium electrode. In addition to BSA, the final suspension contained bovine fibrinogen 25 mg dl^{-1} (Calbiochem, fraction I). All solutions used in this separation contained apyrase 7 mg dl^{-1} (Sigma Chemical) to degrade any ADP released by damaged platelets (Ardlie et al., 1971). Because of the Tris buffer system, 5% carbon dioxide was not required to maintain a physiological pH.

After transferring 0.5 ml of the 200 000-μl^{-1} platelet suspension to a 16-mm round bottom tube in a 37 °C bath, halothane vapour was passed over the surface of the suspension at 100 ml min^{-1}. Halothane was vaporized in a copper kettle with 5% carbon dioxide in air except for the albumin density gradient separated (ADGS) platelet study, in which air was used. Concentrations were verified by a Miran 1 A Infrared Analyzer at 3.30 μm. Mixing of the plasma was by low amplitude oscillation at a frequency of 140 min^{-1}, sufficient to achieve a maximal effect after 15 min.

Four-tenths millilitre of the equilibrated aliquot was then transferred to a siliconized, transmission-matched cuvette in a Sienco model DP-247E platelet aggregation meter and stirred at 1000 rev min^{-1}. ADP 10 μl (Sigma Chemical) was added to induce aggregation, yielding a final ADP concentration of 50 μmol litre^{-1}. For each assay the ratio of change in light transmission with aggregation to the difference in light transmission between PRP and PFP was calculated. The residual activity was the ratio found in an aliquot after exposure to halothane compared with the ratio calculated for the control aliquot of the same specimen incubated and handled in the same manner. Statistical evaluation of the halothane suppression data for the four preparations was made using two-way analysis of variance with appropriate contrasts.

RESULTS

It was found that halothane induced a dose-related suppression of ADP-induced platelet aggregation ($P < 0.001$) (fig. 1). By orthogonal comparisons with coefficients corrected for unequal spacing of halothane

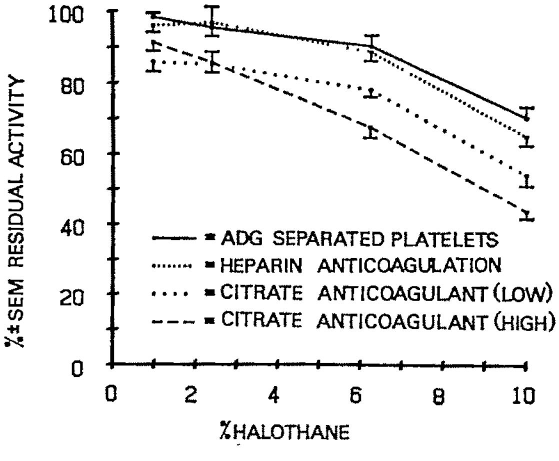

FIG. 1. Residual activity (and SEM) after exposure to halothane for the four types of preparation studied. The albumin density gradient (ADG) separated platelets required no anticoagulant. The final concentrations of anticoagulant in the heparin, low citrate and high citrate preparations were sodium heparin 2 u. ml^{-1}, sodium citrate 6.8 mmol litre^{-1} (2% w/v) and 13.6 mmol litre^{-1} (4% w/v) respectively; 100% indicates a response after halothane identical to that of the control. Each point is the mean of results from seven donors.

concentrations, the suppression has a linear dependence on the dose of halothane ($P<0.001$). For the two preparations with no calcium chelation, no inhibition occurred at the two halothane concentrations in the clinical range ($P>0.05$). Fifty per cent inhibition was achieved only at very high concentrations of halothane, about 9%, with calcium chelation by sodium citrate 13.6 mmol litre^{-1}. With half as much sodium citrate, 6.8 mmol litre^{-1}, the 50% inhibitory dose increased to more than 10% halothane.

The halothane suppression in the heparin and ADGS preparations did not differ when compared by analysis of variance with contrasts ($P>0.30$). The ionized calcium concentration (mean ± SEM) of the heparinized preparations was in the normal range, 0.991 ± 0.014 mmol litre^{-1}. This was not different from the concentration after adjustment with calcium chloride in the ADGS platelet suspension, 0.986 ± 0.008 mmol litre^{-1}. The preparations with a normal calcium ion concentration were suppressed significantly less by halothane than either the 6.8-mmol litre^{-1} citrate preparation ($P<0.001$) or the 13.6-mmol litre^{-1} citrate preparation ($P<0.001$).

Other variables were verified also for the halothane effect studied. The pH of the determinations in figure 1 was well within the physiological range. The two preparations with normal calcium ion concentrations, heparin and ADGS platelets, had a pH of 7.465 ± 0.011 unit (mean ± SEM). Equilibrium with the methods used was achieved at 15 min (fig. 2), since no additional inhibition occurred with additional exposure. The concentration of ADP, 50 μmol litre^{-1}, was selected in the same manner as by Ueda (1971); that is, the minimum ADP concentration required to prevent deaggregation. However, when the ADP concentration was varied (fig. 3), the 50 μmol litre^{-1} concentration resulted in inhibition not significantly different from 25 μmol litre^{-1} which produced the maximum inhibition ($P>0.20$).

Figure 4 shows the levels of activity of PRP with sodium citrate 13.6 mmol litre^{-1} after 15 min exposure to halothane followed by 10 min exposure to the

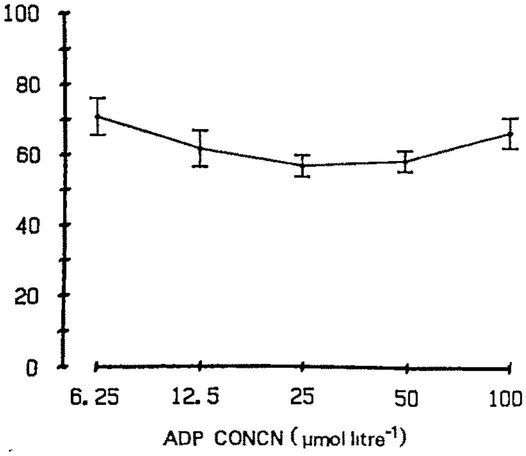

FIG. 3. Effect of altering the ADP concentration on residual activity after 6.1% halothane treatment of platelets in 13.6-mmol litre^{-1} citrated plasma. Each point represents the mean of five preparations from a single donor.

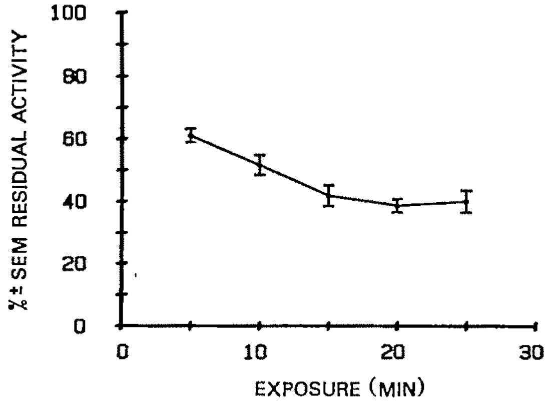

FIG. 2. Effect of exposure time on residual activity of a 13.6-mmol litre^{-1} citrated specimen exposed to halothane 10.1%. The sum of incubation time with halothane plus incubation time with carrier gas was 25 min for all aliquots. Each point represents seven preparations from a single donor.

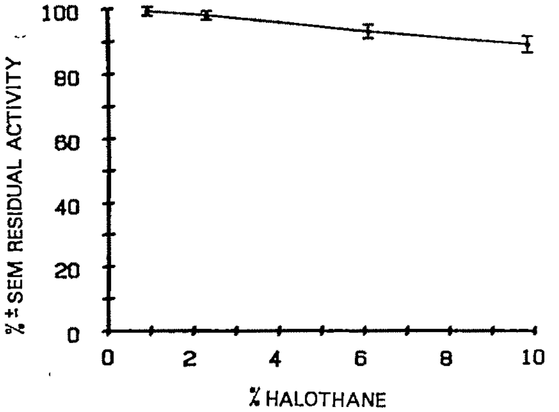

FIG. 4. Reversal of the effect of halothane on platelets in 13.6-mmol litre^{-1} citrated plasma. Exposure to halothane for 15 min followed by 10 min flush with carrier gas. Controls were incubated in carrier gas for 25 min. Each point represents the mean of results from seven donors.

carrier gas alone. At the two clinical concentrations, reversal was complete ($P > 0.05$). Minimal depression at high concentrations of halothane did remain after 10 min.

DISCUSSION

When methods for the study of *in vitro* platelet function were adjusted to simulate the physiological *in vivo* condition, an order of magnitude difference was found for the halothane concentration causing 50% inhibition of ADP-induced aggregation. The enhancement of anaesthetic potency at low temperatures (Eger, Saidman and Brandstater, 1965) may have been the primary cause of the failure to demonstrate inhibition at 37 °C at clinical concentrations while Ueda (1971) observed inhibition at 25 °C. Han and Ardlie (1974) predicted that platelets stored at room temperature were sensitized to ADP, and we used a greater concentration of ADP to induce aggregation in this study, since platelets were maintained at 37 °C. The reversibility of the equilibrated suspensions suggests a drug effect rather than destruction by handling and equilibration methods, although the remaining minimal suppression at high halothane concentrations may have represented insufficient removal of halothane or a component of irreversible change.

Platelet aggregation in response to ADP is dependent on the concentration of calcium and may be inhibited completely by high concentrations of citrate for anticoagulation (Skoza et al., 1967). Feinstein, Fiekers and Fraser (1976) have shown that inhibition of platelet aggregation by local anaesthetic agents is in part dependent on the calcium ion concentration. Although varying the citrate concentration confirmed the dependence of halothane suppression of platelet aggregation on a calcium chelating anticoagulant, the experiment did not distinguish between the effect of the citrate anion and that of the low calcium cation. Heparin does prevent coagulation and allow normal calcium concentrations, but may cause aggregation (Zucker, 1977). This problem was not apparent since a low concentration of heparin was used and aggregates present may have been broken up by mixing during incubation. Resuspension of platelets in a procoagulant-deficient solution required no anticoagulants, but the advantage of studying platelets in a minimally altered chemical environment was lost. The results, however, were equivalent to those obtained when heparin was present.

Our data represent only one aspect of platelet function and were obtained by an *in vitro* method. ADP-induced aggregation does not reveal directly the effect of halothane on the platelet release reaction. If a high concentration of halothane or halothane plus calcium chelation did suppress the release reaction, less suppression would have been expected when small amounts of ADP were used, since release would have been minimal (note, for example the assays with low ADP (fig. 3)). Perhaps halothane would have a significant role in collagen-induced aggregation which is more dependent on the release reaction. No benign *in vivo* assay of platelet function analogous to the method of Born (1962) has gained wide acceptance. The observation (Harker et al., 1976) that *in vitro* platelet function tests and *in vivo* antithrombotic effects of drugs have had a variable correlation may be a result of poor control of experimental conditions such as those considered in this investigation.

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ECHEC DES CONCENTRATIONS CLINIQUES D'HALOTHANE POUR BLOQUER L'AGREGATION DE GLOBULINS PROVOQUEE PAR LE DIPHOSPHATE D'ADENOSINE *IN VITRO*

RESUME

On a mesuré l'inhibition obtenue en fonction de la dose d'halothane, d'une agrégation de globulins provoquée par le diphosphate d'adénosine, pour des globulins humains se trouvant dans du plasma non coagulé, grâce à du citrate de soude, à raison de 6,8 mmol litre^{-1} ou de 13,6 mmol litre^{-1} de citrate de soude ou de 2 u. ml^{-1} d'héparine, de même que pour les globulins séparés du plasma par centrifugation du gradient de densité de l'albumine, et sans anticoagulant. En maintenant la température de l'exposition et de l'essai de conformité à 37 °C, en maintenant le pH physiologique, en évitant la détérioration lieé à l'âge et en utilisant une méthode d'équilibrage atraumatique, on n'a trouvé aucune inhibition aux concentrations cliniques d'halothane, et 50% d'inhibition aux concentrations d'halothane supérieures à 10%. Le citrate de soude, qui est un agent complexant anticoagulant du calcium, augmente l'inhibition de l'halothane.

DIE UNFÄHIGKEIT KLINISCHER KONZENTRATIONEN VON HALOTHAN, DIE DURCH ADENOSIN DIPHOSPHAT EINGELEITETE ZUSAMMENBALLUNG *IN VITRO* VON BLUTPLÄTTCHEN ZU BLOCKIEREN

ZUSAMMENFASSUNG

Eine dosisbezogene Unterdrückung der durch Adenosin Diphosphat eingeleiteten Zusammenballung von Blutplättchen mittels Halothan wurde bei menschlichen Plättchen in Plasma gemessen, das durch 6,8 mmol Liter^{-1} Natriumzitrat, oder durch 13,6 mmol Liter^{-1} Natriumzitrat, oder durch 2 u. ml^{-1} Heparin am Gerinnen gehindert wurde, sowie bei vom Plasma getrennten Blutplättchen durch eine Albumindichte-Zentrifugierung, wobei kein Anti-Gerinnungsmittel erforderlich war. Bei gleichbleibender Aussetzung und Testtemperatur von 37 °C, gleichbleibendem physiologischem pH und bei Vermeidung eines altersbezogenen Verfalls sowie unter Verwendung einer atraumatischen Gleichgewichtsmethode wurde bei klinischen Halothan-Dosen keine Unterdrückung festgestellt, und eine Unterdrückung von 50% erforderte mehr als 10% Halothan. Natriumzitrat, ein Kalzium Chelate-Anti-Gerinnungsmittel, erhöhte die Halothan-Unterdrückung.

INCAPACIDAD DE BLOQUEAR LA AGREGACION DE PLAQUETAS, INDUCIDA POR DIFOSFATO DE ADENOSINA, MEDIANTE CONCENTRACIONES CLINICAS DE HALOTANO *IN VITRO*

SUMARIO

Se midió la inhibición relacionada con dosis de halotano en la agregación de plaquetas, inducida por difosfato de adenosina, para plaquetas humanas en plasma anticoagulada con 6,8 mmol litro^{-1} de citrato sódico, 13,6 mmol litro^{-1} de heparina y para plaquetas separadas de la plasma por centrifugación de gradiente a densidad de albúmina, que no requieren anticoagulante. Manteniendo la temperatura de exposición y prueba a 37 °C, conservando el pH fisiológico, evitando el deterioro relacionado con la edad y aplicando un mátodo de equilibrio atraumático, no se descubrió inhibición alguna a concentraciones clínicas de halotano, y un 50% de inhibición requirió más de un 10% de halotano. Se descubrió que el citrato sódico, un anticoagulante quelator de calcio, aumenta la inhibición de halotano.

Br. J. Anaesth. (1979), **51**, 193

CANINE CORONARY BLOOD FLOW RESPONSES TO HYPOXAEMIA: THE INFLUENCE OF HALOTHANE

J. P. VANCE, D. M. BROWN, G. SMITH AND J. THORBURN

SUMMARY

Electromagnetic flow meters were used to measure blood flow in the coronary and pulmonary arteries of six anaesthetized dogs following thoracotomy. Halothane 1% (v/v) caused a reduction in arterial pressure, coronary artery flow, cardiac output and myocardial and total body oxygen consumption and an increase in coronary vascular resistance. Hypoxaemia caused large increases in coronary artery flow during both cardiac systole and diastole, but not until Pa_{O_2} was less than 5.3 kPa. This response was not influenced by the presence of halothane. Although myocardial oxygen availability and consumption were maintained during hypoxaemia, total body oxygen availability and consumption were markedly reduced.

Hypoxaemia is a potent stimulus to myocardial blood flow (Berne, Blackmon and Gardner, 1957; Feinberg, Gerola and Katz, 1958; Aukland et al., 1967; Vance, Parratt and Ledingham, 1971). Halothane causes a decrease in myocardial blood flow, especially when hypotension is induced (Merin, 1969; Weaver, Bailey and Preston, 1970; Smith et al., 1974), and an increase in vascular resistance within the myocardium (Wolff et al., 1972; Smith et al., 1974; Vance et al., 1975).

The coexistence of increased myocardial vascular resistance with arterial hypotension during halothane administration in dogs has prompted us to examine blood flow in response to hypoxaemia under similar circumstances. A series of dogs was subjected to increasing degrees of hypoxaemia without and subsequently in the presence of halothane and the changes in myocardial and systemic haemodynamics and oxygen handling were observed.

METHOD

Six dogs of mixed breed (weight range 14–20 kg) were anaesthetized with thiopentone 20 mg kg^{-1}. The trachea was intubated with the aid of suxamethonium 50–100 mg i.v. Ventilation of the lungs with oxygen was commenced at a rate of 20 b.p.m. from a Palmer sine wave pump. The tidal volume was adjusted to maintain Pa_{CO_2} at about 5.3 kPa. Thereafter pentobarbitone sodium 30 mg kg^{-1} was administered i.v. Each animal was placed in the right lateral position and, with the aid of an image intensifier catheters were inserted into the descending thoracic aorta via the right femoral artery, the right atrium via the right femoral vein, the pulmonary artery and the left ventricle via the left common carotid artery.

A left thoracotomy was performed and close-fitting flow transducers were applied to a major branch of the left coronary artery and to the pulmonary artery (Statham SP 7515 and 7516). These were connected to flow meters with a non-occlusive zero facility (Statham SP 2202).

The left lung was re-inflated and positive end-expiratory pressure of 5 cm H_2O was applied to maintain lung inflation. The inspired oxygen fraction (FI_{O_2}) was adjusted by adding nitrogen so that Pa_{O_2} was about 13.3 kPa; the temperature of the animal was maintained at 37 °C ± 1 °C by electric lamps. When all values were stable for 5–10 min, the following readings and samples were taken: aortic, right atrial, left ventricular and pulmonary artery (PA) pressures (using suitably calibrated Elema Schonander transducers). Heart rate was counted from the e.c.g. All of the above, and coronary and pulmonary artery flow and left ventricular dp/dt, were recorded as tracings using a multi-channel ink jet recorder (Elema Schonander). Arterial, coronary sinus and pulmonary artery (mixed venous) blood was sampled for measurement of haemoglobin concentration using a co-oximeter (Instrumentation Laboratories I.L. 213) and Po_2, Pco_2 and pH using suitably

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calibrated electrode systems (Instrumentation Laboratories I.L. 182).

FI_{O_2} was reduced progressively so that readings and samples could be obtained with Pa_{O_2} at about 7 kPa, 5 kPa and 3.5 kPa. FI_{O_2} was then returned to control and, when all variables had stabilized at ± 10% of their previous control value for not less than 10 min, halothane 1% (v/v) was added to the inspired mixture from a previously calibrated Mk II Fluotec vaporizer (Cyprane). Thereafter, when all variables had stabilized for 5 min (a total mean time of 21 min of halothane administration), the hypoxic stimuli were repeated and further readings and samples taken.

Each exposure to hypoxaemia lasted until the new value of Pa_{O_2} was stable for 5 min, except in those instances where a major change in coronary artery flow occurred, when hypoxaemia was maintained until the flow changes were maximal (usually 2–3 min at the new Pa_{O_2}).

Blood oxygen content was calculated from Po_2 taking into account haemoglobin concentration, body temperature and blood pH.

The following were calculated:

Myocardial oxygen extraction (%) =

$$\frac{Ca_{O_2}-Ccs_{O_2}}{Ca_{O_2}} \times \frac{100}{1}$$

Myocardial oxygen availability (ml min^{-1}) =

$$\frac{Ca_{O_2} \times \text{CAF (mean)}}{100}$$

Myocardial oxygen consumption (ml min^{-1}) =

$$\frac{(Ca_{O_2}-Ccs_{O_2}) \times \text{CAF (mean)}}{100}$$

Total body oxygen extraction (%) =

$$\frac{Ca_{O_2}-C\bar{v}_{O_2}}{Ca_{O_2}} \times \frac{100}{1}$$

Total body oxygen availability (ml min^{-1}) =

$$Ca_{O_2} \times \text{CO} \times 10$$

Total body oxygen consumption (ml min^{-1}) =

$$(Ca_{O_2}-Cmv_{O_2}) \times \text{CO} \times 10$$

Myocardial vascular resistance (units) =

$$\frac{P\bar{a}-P\bar{a}_r}{\text{CAF}} \times \frac{10}{1}$$

Total vascular resistance (units) =

$$\frac{(P\bar{a}-P\bar{a}_r)}{\text{CO}} \times \frac{10}{1}$$

dp/dt max (mm Hg s^{-1}) was derived by electronic differentiation of the left ventricular pressure trace.

Ca_{O_2} = arterial oxygen content (ml dl^{-1})

Ccs_{O_2} = coronary sinus oxygen content (ml dl^{-1})

$C\bar{v}_{O_2}$ = mixed venous (pulmonary arterial) oxygen content (ml dl^{-1})

CAF = coronary arterial flow (ml min^{-1})

CO = cardiac output (litre min^{-1})

$P\bar{a}$ = mean arterial (aortic) pressure (mm Hg)

$P\bar{a}_r$ = mean right atrial pressure (mm Hg)

In the calculation of systolic, diastolic and mean myocardial vascular resistance, the appropriate phasic values for pressures and flow were utilized. It is assumed for the above calculations that coronary sinus blood is representative of the venous outflow of the area of myocardium perfused by the artery in which flow was measured.

The mean and SEM for each variable at each value of Pa_{O_2}, without and with halothane, were calculated. The data with and without halothane were compared for each value of Pa_{O_2} using Student's t test for paired data (table I). $P < 0.05$ was regarded as significant (* in table). Each variable at each Pa_{O_2} was compared with its own control measurement (Pa_{O_2} at normal value) in a similar manner ($P < 0.05$ indicated †).

RESULTS

The administration of halothane was associated with a marked decrease in coronary artery flow (mean, systolic and diastolic) compared with the results before administration of halothane. The various levels of hypoxaemia caused increases in coronary flow in a pattern which was independent of the presence of halothane. The maximum recorded increases occurred when Pa_{O_2} was about 3.5 kPa (101% mean flow increase without halothane and 153% with halothane; 61 and 120% for systolic flow, 69 and 113% for diastolic flow). Although there were increases in arterial pressure (perfusion pressure) at the lower values of Pa_{O_2}, this did not account entirely for the very large increases in

TABLE I. *All variables are shown as mean ± SEM for six dogs*

	Without halothane			
Pa_{O_2} (kPa)	13.0 ± 0.1	7.1 ± 0.3	4.9 ± 0.3	3.7 ± 0.2
Pa_{O_2} (mm Hg)	99 ± 0.8	54 ± 2.3	37.2 ± 2.3	28.1 ± 1.5
Mean arterial pressure (mm Hg)	136 ± 14.7	138 ± 13	150 ± 14	157 ± 12†
Heart rate (beat min^{-1})	155 ± 14	159 ± 13	165 ± 12	170 ± 11
Mean CAF (ml min^{-1})	99 ± 19	109 ± 25	145 ± 30†	200 ± 39†
Systolic CAF (ml min^{-1})	50 ± 15	57 ± 16	82 ± 24†	127 ± 26†
Diastolic CAF (ml min^{-1})	153 ± 43	165 ± 50	198 ± 50	258 ± 64†
Myocardial O_2 consumption (ml min^{-1})	13.7 ± 3.7	13.4 ± 4.0	14.6 ± 4.3	16.4 ± 4.0
Myocardial O_2 availability (ml min^{-1})	23.0 ± 6.9	21.9 ± 7.9	23.3 ± 7.6	24.9 ± 6.8
Myocardial O_2 extraction (%)	62 ± 7	66 ± 7	65 ± 7	70 ± 5
Cardiac output (litre min^{-1})	4.7 ± 0.4	5.3 ± 0.6	5.2 ± 0.2	5.9 ± 0.7†
Total O_2 consumption (ml min^{-1})	279 ± 50	254 ± 53	165 ± 25†	156 ± 28†
Total O_2 availability (ml min^{-1})	1070 ± 159	1037 ± 164	799 ± 81†	656 ± 91†
Total O_2 extraction (%)	26 ± 3	25 ± 4	23 ± 4	24 ± 4
PA pressure (mm Hg)	14 ± 2.3	14 ± 2.0	15 ± 0.21†	15 ± 2.5†
d*p*/d*t* max (mm Hg s^{-1})	2300 ± 329	2440 ± 365	2860 ± 594†	3260 ± 682†
Mean CAR (units)	12.1 ± 2.1	13.0 ± 2.7	10.0 ± 2.1	7.2 ± 1.5†
Systolic CAR (units)	36.6 ± 10	33.5 ± 9	23.0 ± 6†	11.6 ± 2.0†
Diastolic CAR (units)	7.1 ± 1.3	7.1 ± 1.4	6.4 ± 1.4	5.0 ± 1.1†
L.v.e.d.p. (mm Hg)	6.9 ± 1.1	6.8 ± 1.4	6.2 ± 1.0	7.0 ± 1.3
Total vascular resistance	234 ± 23	216 ± 27	232 ± 19	241 ± 35
Coronary sinus Po_2 (kPa)	3.4 ± 0.3	2.7 ± 0.2†	2.5 ± 0.2†	2.0 ± 0.15†
(mm Hg)	26 ± 2.6	21 ± 1.8†	19 ± 1.6†	15 ± 1.2†

	With halothane			
Pa_{O_2} (kPa)	12.8 ± 0.2	6.9 ± 0.1	4.4 ± 0.4	3.3 ± 0.26
Pa_{O_2} (mm Hg)	97 ± 1.5	52 ± 0.8	33.4 ± 3.0	25.1 ± 2.0
Mean arterial pressure (mm Hg)	84 ± 12.5*	81 ± 13*	92 ± 14*	102 ± 15*†
Heart rate (beat min^{-1})	135 ± 12*	130 ± 14*	133 ± 13*	149 ± 12*
Mean CAF (ml min^{-1})	50 ± 17*	51 ± 19*	67 ± 18*	126 ± 29*†
Systolic CAF (ml min^{-1})	21 ± 10*	20 ± 8*	27 ± 12*	81 ± 20*†
Diastolic CAF (ml min^{-1})	81 ± 30*	81 ± 31*	94 ± 21*	172 ± 56*†
Myocardial O_2 consumption (ml min^{-1})	7.19 ± 2.8*	6.7 ± 2.5*	6.5 ± 1.7*	7.6 ± 2.6*
Myocardial O_2 availability (ml min^{-1})	11.4 ± 5.8*	9.9 ± 4.6*	9.6 ± 2.3*	11.0 ± 4.4*
Myocardial O_2 extraction (%)	65 ± 5	66 ± 5	68 ± 6	72 ± 4
Cardiac output (litre min^{-1})	3.1 ± 0.2*	3.2 ± 0.2*	3.5 ± 0.35*	5.5 ± 0.5†
Total O_2 consumption (ml min^{-1})	190 ± 19*	179 ± 30	169 ± 44	122 ± 19†
Total O_2 availability (ml min^{-1})	697 ± 91*	633 ± 62*	522 ± 72*†	398 ± 69*†
Total O_2 extraction (%)	28 ± 3	28 ± 4	31 ± 6	29 ± 5
PA pressure (mm Hg)	11 ± 2.2	12 ± 2.2	12 ± 2.6*	15 ± 3.3†
d*p*/d*t* max (mm Hg s^{-1})	1580 ± 289*	1280 ± 136*	1580 ± 201*	1860 ± 344*
Mean CAR (units)	17.4 ± 2.2*	14.5 ± 2.2	11.1 ± 1.3†	7.4 ± 1.6†
Systolic CAR (units)	59.2 ± 5.5*	41.0 ± 4.6†	31.7 ± 4.1†	18.1 ± 3.2†
Diastolic CAR (units)	8.8 ± 1.3	8.1 ± 1.6	6.5 ± 0.9	4.7 ± 1.4†
L.v.e.d.p. (mm Hg)	6.2 ± 0.6	7.4 ± 0.8	8.7 ± 2.0	8.0 ± 1.4
Total vascular resistance	213 ± 23	205 ± 32	209 ± 21	173 ± 19
Coronary sinus Po_2 (kPa)	2.9 ± 0.13	2.6 ± 0.13	2.1 ± 0.14†	1.5 ± 0.2†
(mm Hg)	22 ± 1.0	20 ± 1.0	16 ± 1.1†	11.2 ± 1.6†

* Significant differences ($P < 0.05$) between values with halothane and corresponding values without halothane.

† Significant differences between any value and its own control (normal Pa_{O_2}).

CAR = Coronary artery resistance.

coronary flow, since there were, in addition, considerable reductions in coronary arterial resistance indicating coronary vasodilatation.

Cardiac output increased by 77 and 26.5% (halothane and non-halothane) in response to the most severe degree of hypoxaemia.

Total vascular resistance did not alter in response to hypoxaemia in the absence of halothane although there was a marked reduction with halothane (19% at Pa_{O_2} 3.3 kPa). In spite of an increase in cardiac output at low Pa_{O_2}, the total body oxygen availability decreased, as did total oxygen consumption. Myocardial oxygen availability was maintained during hypoxaemia as was myocardial oxygen consumption.

Left ventricular end-diastolic pressure showed little change with hypoxaemia; however left ventricular d*p*/d*t* showed marked increases independent of halothane.

DISCUSSION

This study confirms that halothane administration in the dog is associated with a reduction in coronary artery flow and an increase in coronary vascular resistance. The increase in vascular resistance is most marked during the systolic phase of the myocardial cycle, despite a considerable reduction in d*p*/d*t* max during halothane administration (which might be expected to lead to a reduction in systolic vascular resistance since the extravascular component of the resistance will be lessened).

The reduction in Pa_{O_2} was associated with a large increase in coronary arterial flow, but not until Pa_{O_2} was less than 5.3 kPa (40 mm Hg). This response was independent of halothane. This suggests that the coronary flow response to decreasing Pa_{O_2} is not linear and that there is a critical level of hypoxaemia at which large coronary flow increases occur, a finding in keeping with previous work (Berne, Blackmon and Gardner, 1957; Vance, Parratt and Ledingham, 1971). It was of interest that the percentage increase in flow at the smallest Pa_{O_2} was greater with halothane than without halothane, this effect being most marked during systole.

The quantity of oxygen available to the myocardium did not change significantly throughout the experiment and therefore the increase which occurred in oxygen consumption at the lowest value of Pa_{O_2} without halothane was possible only because of an increase in myocardial oxygen extraction. It has been suggested that the myocardium always works at maximum oxygen extraction, but this is obviously not so, at least during anaesthesia. It is of interest to note that when Pa_{O_2} was at its lowest the mean coronary sinus Po_2 was 2 kPa (without halothane) and 1.46 kPa (with halothane).

The systemic changes noted in response to hypoxaemia were predictable. Arterial pressure, cardiac output, heart rate and d*p*/d*t* max all increased. The increase in cardiac output, however, was not sufficient to maintain the total oxygen availability at the pre-hypoxaemic value and both this and the total oxygen consumption decreased whether or not halothane was administered. This emphasizes the preferential perfusion of vital tissues such as the heart during hypoxaemia. The fact that the total fraction of oxygen extracted did not alter during hypoxaemia indicates a shunting of blood away from less vital tissues. It is noteworthy that halothane did not interfere with this process.

Although the mean percentage increase in cardiac output at lowest Pa_{O_2} was much greater with (77%) than without halothane (25%), the related reductions in total oxygen availability (43% and 39%) and consumption (36% and 44%) were similar.

An increase in pulmonary vascular resistance in response to hypoxaemia is a well-recognized phenomenon (Duke, 1957). Sykes and his co-workers (1972) have suggested from studies of perfused cat and dog lung that this response is abolished by certain anaesthetic agents including halothane 5% (v/v) and Loh, Sykes and Chakrabarti (1977) have observed an effect at 3% (v/v). If this work can be extrapolated to the present study, then one must assume that the increase noted in pulmonary artery pressure during hypoxaemia with halothane was a result of the increasing cardiac output.

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REACTIONS DU DEBIT SANGUIN CORONAIRE DES CHIENS A L'HYPOXIE: INFLUENCE DE L'HALOTHANE

RESUME

On a mesuré, à l'aide de débitmètres électromagnétiques, le débit sanguin des artères coronaire et pulmonaire après thoracotomie, sur six chiens anesthésiés. L'introduction de 1% d'halothane dans le mélange (v/v) a provoqué une réduction de la pression artérielle, du débit de l'artère coronaire, de la fréquence cardiaque ainsi que de la consommation d'oxygène du myocarde et de celle de l'ensemble du corps; elle a également provoqué une augmentation de la résistance vasculaire coronaire. L'h poxémie a provoqué de fortes augmentations dans le débit de l'artère coronaire aussi bien pendant la systole que pendant la diastole cardiaques, mais cela ne s'est produit qu'après que la Pa_{O_2} soit tombée à moins de 5,3 kPa. Cette réaction n'a pas été influencée par la présence d'halothane. Bien que l'on ait maintenu la disponibilité et la consommation d'oxygène du myocarde pendant l'hypoxémie, la disponibilité et la consommation d'oxygène de l'ensemble du corps ont été considérablement réduites.

RFAKTIONEN DES KORONARGEFASS-BLUTFLUSSES AUF HYPOXAMIE BEI HUNDEN: DER EINFLUSS VON HALOTHAN

ZUSAMMENFASSUNG

Elektromagnetische Strömungsmesser wurden zur Messung des Blutflusses in den Herz- und Lungenarterien von sechs anästhesierten Hunden nach Brustraumeröffnung verwendet Halothan (1%) bewirkte Verringerungen bei arteriellem Druck, arteriellem Koronardurchfluss, Herzminutenvolumen sowie myokardialem und Gesamtkörper-Sauerstoffverbrauch, und einen Anstieg des Koronargefässwiderstandes. Hypoxämie verursachte starke Anstiege im arteriellen Koronardurchfluss sowohl bei Systole als auch Diastole des Herzens, aber erst dann, wenn Pa_{O_2} geringer als 5,3 kPa war. Diese Reaktion war durch die Anwesenheit von Halothan nicht beeinflusst. Obwohl die Verfügbarkeit von myokardialem Sauerstoff ebenso wie der Verbrauch während Hypoxämie bewahrt wurden, waren Sauerstoffverfügbarkeit und Verbrauch im ganzen Körper deutlich verringert.

RESPUESTAS DE LA CIRCULACION DE SANGRE EN LA ARTERIA CORONARIA CANINA ANTE HIPOXEMIA: LA INFLUENCIA DE HALOTANO

SUMARIO

Se utilizaron flujómetros electromagnéticos para medir la circulación de sangre en las arterias coronaria y pulmonar de seis perros anestesiados, después de someterlos a toracotomía. Un 1% de halotano (v/v) causó una reducción en la presión arterial, circulación en la arteria coronaria, rendimiento cardíaco y consumo de oxígeno del miocardio y total del cuerpo, y un aumento en la resistencia vascular coronaria. La hipoxemia causó un gran aumento en la circulación arterial coronaria, tanto durante el sístole como el diástole cardíacos, pero no antes que el Pa_{O_2} fuera inferior a 5,3 kPa. Esta respuesta no fue influenciada por la presencia de halotano. Aunque la disponibilidad y consumo de oxígeno del miocardio fueron mantenidos durante la hipoxemia, la disponibilidad y consumo total de oxígeno en el cuerpo fueron marcadamente reducidos.

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PERFORMANCE OF A SHELL-TYPE HEAT EXCHANGER IN EXTRACORPOREAL CIRCULATION

K. A. FLOWER, E. A. SHAW AND P. MORRIS

SUMMARY

Tests were performed on a "shell" type heat exchanger used in a simulated extracorporeal circulation. The counter flow mode was the most efficient pattern and recommendations are made on which flow pattern should be employed with low water flow rates.

We have investigated some of the factors affecting heat exchanger performance in a laboratory simulation of a paediatric extracorporeal circulation. Measurements have been made of water flow rate, blood flow rate, temperature gradients and directional flows of water and blood within the heat exchanger. The shell-type Rygg–Kyvsgaard heat exchanger has been used at the Royal Manchester Children's Hospital during open heart surgery and its performance was studied with normal and varying patterns of water flow. The design of this heat exchanger is such that alteration of the pattern of water flow could be achieved easily.

The heat exchanger has three functions: to maintain normothermia, to induce varying degrees of hypothermia and to restore normothermia. These objectives are achieved by a secondary circuit of hot or cold water passing in close proximity to the flow of blood through the heat exchanger. To produce a blood stream surrounded by a water stream, some extracorporeal heat exchangers use the shell technique which employs an inner core and an outer jacket water flow, all of the fluid streams being confined to concentric annuli. The commercially available shell-type heat exchangers channel the water from the inner core through the outer jacket before going to waste.

A schematic diagram of the normal flow pattern within the Rygg–Kyvsgaard heat exchanger is shown in figure 1. The flexible pipe connection of the Rygg–Kyvsgaard heat exchanger, from the inner core to the outer jacket, presents the facility whereby the pattern of water flow may be changed. Adjustments of the plumbing allowed this heat exchanger to be used with the following water flow patterns:

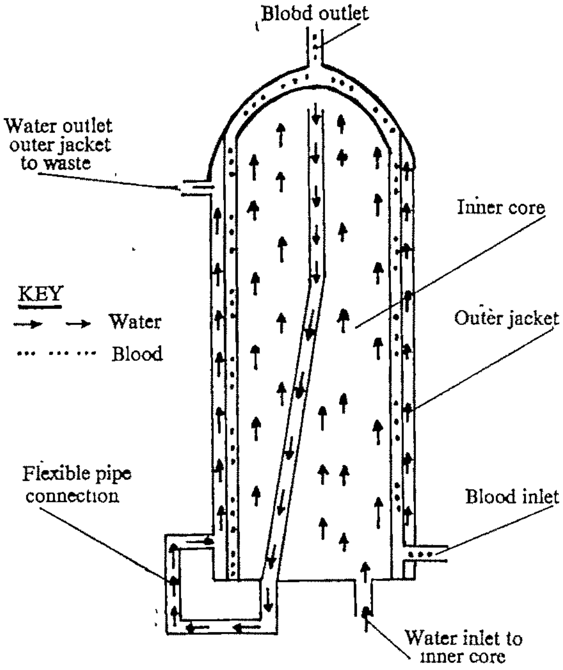

FIG. 1. Parallel inner core, parallel outer jacket, double pass water flow.

(1) Parallel inner core flow, parallel outer jacket flow —normal mode.
(2) Parallel inner core flow, counter outer jacket flow.
(3) Counter inner core flow, parallel outer jacket flow.

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In all of these modes the water from the inner core passes through the outer jacket before being exhausted to waste. This is described as a double pass to the blood flow. However, this can be changed to a single pass system. An example of a counter inner core flow, counter outer jacket flow single pass mode is illustrated in figure. 2.

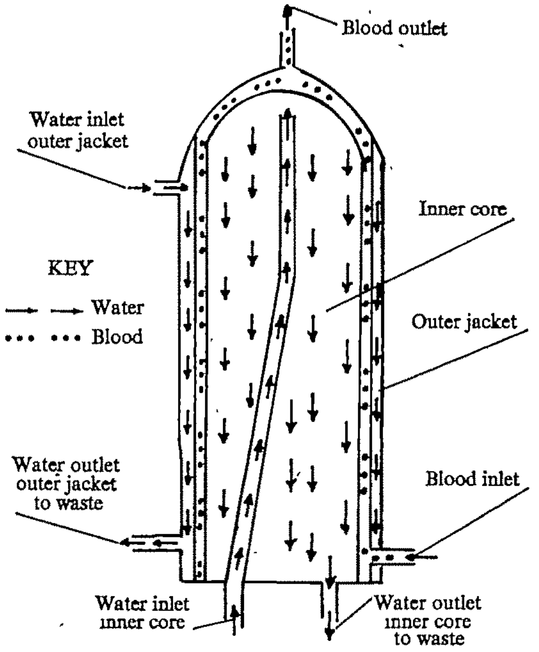

FIG. 2. Counter inner core flow, counter outer jacket flow, single pass.

An extracorporeal circulation requires a small heat exchanger with a low blood priming volume and small temperature differences. Bethune, Gill and Wheeldon (1975) recommended that water flow rates of 15–20 litre min^{-1} at 140 kPa should be available in cardiothoracic theatres, but this is rare at present. This study was undertaken to investigate heat exchanger performance with small water flow rates (2.5–8.0 litre min^{-1}), blood flow rates of 1.27–3.8 litre min^{-1} and variable patterns of water flow.

APPARATUS AND PROCEDURE

A schematic diagram of the laboratory model of a paediatric extracorporeal circuit is shown in figure 3. The following procedures were carried out in sequence:

(1) The water flow pattern through the heat exchanger was arranged by adjustment of the plumbing (figs 1, 2).

(2) The blood circuit was primed with 1 litre of time-expired blood and 1 litre of 0.9% sodium chloride solution.

(3) Water at 42 °C was passed through the heat exchanger until the entire blood circuit attained a temperature of 41 °C.

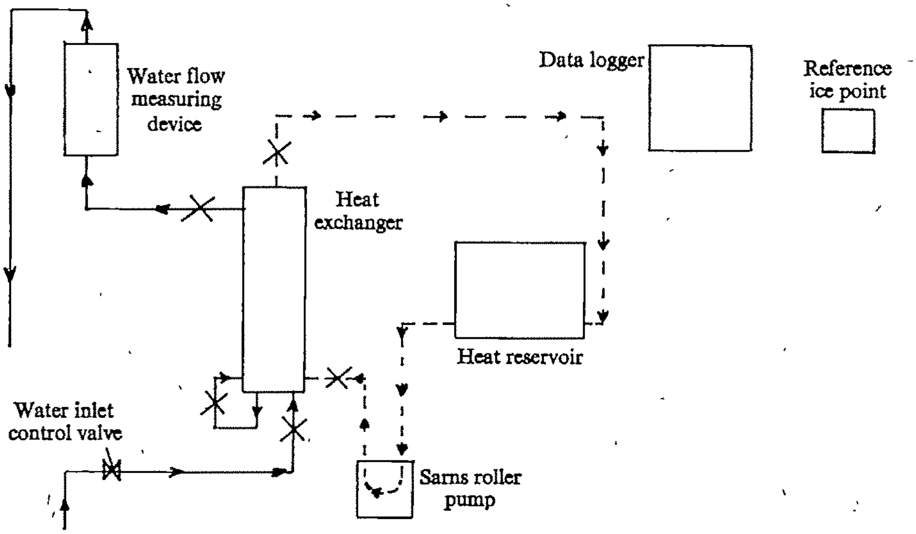

FIG. 3. Schematic of the laboratory simulation of a paediatric extracorporeal circuit. X = instream Cr/Al T1–T2 thermocouple junctions connected to the data logger.

(4) The Sarns roller pump (Model 3500) was switched on to give a prescribed blood flow rate through the circuit.
(5) The Data Logger (Schlumberger–Solaratron Data logger with a series 3 analog scanner driving a Facit 4070 tape punch) was started and a punched tape record of all the thermocouple temperature monitors, including the ambient laboratory temperature, was made very 4 s.
(6) Cold water at 12 °C was turned on and the flow rate adjusted to a prescribed value.
(7) The test was allowed to proceed until the blood inlet temperature had decreased to 17 °C.
(8) The test procedure (3–7) was repeated until the series of tests (table I) for each particular mode of water flow had been completed.
(9) The punch tape data were analysed on a DEC 1145 computer and the heat extracted from the blood over the duration of each test calculated.
(10) The water flow pattern through the heat exchanger was then adjusted to each of the other modes and the test procedure 2–9 repeated for each mode.

TABLE I. *Summary of the tests. A = Parallel inner core, parallel outer jacket (normal mode); B = counter inner core, counter outer jacket; C = counter inner core, counter outer jacket (single pass); D = parallel inner core, counter outer jacket (single pass); E = counter inner core, parallel outer jacket (single pass); F = counter inner core, parallel outer jacket; G = parallel inner core, counter outer jacket*

Water flow rate (litre min^{-1})	Blood flow rate (litre min^{-1})		
	1.27	2.54	3.81
2.5	ABC DEFG	ABC DEFG	AB
4.0	ABG	B	A
4.5	ABCDF	CE	B
6.0	AB	B	AB
8.0	AB		

RESULTS

Details of the experimental programme are given in table I. The blood flow rates used (1.27, 2.54 and 3.81 litre min^{-1} in table I) are related to the calibration scale on the Sarns Roller Pump (1.27 litre min^{-1} corresponds to the 20 division mark on the pump scale).

Thirty-six individual tests were performed (table I). Four test sequences are reproduced in table II, which shows the total heat extracted with time for a blood flow rate of 1.27 litre min^{-1} and a double pass water flow rate of 2.5 litre min^{-1}. These four tests are represented graphically in figure 4.

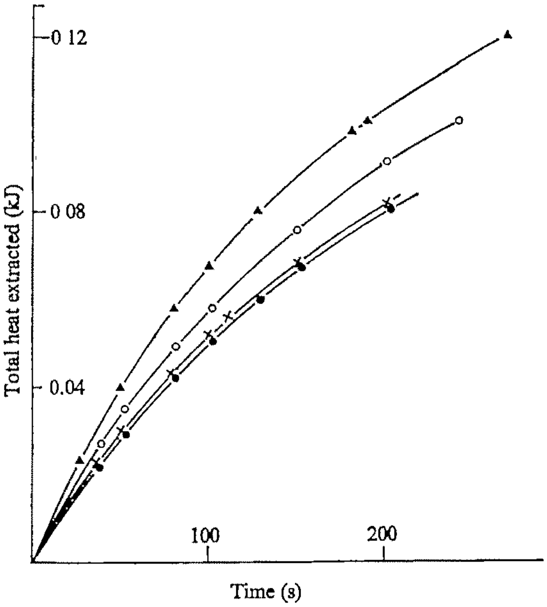

FIG. 4. Total heat extracted *v.* time with water flow rate 2.5 litre min^{-1}, blood flow rate 1.27 litre min^{-1}. *Flow pattern*: Inner core— ● = parallel, ○ = parallel, × = counter, ▲ = counter. Outer jacket— ● = parallel, ○ = counter, × = parallel, ▲ = counter.

The comparative efficiencies of the five modes of water flow pattern through the heat exchanger are shown in figure 5. The normal mode (fig. 1) is shown as the 100% datum and is the least efficient of these modes; the best double pass mode was equivalent to 132%. The single pass counter mode was 97% more efficient than the normal mode and 65% more efficient than the best double pass mode. The efficiency increased with the water flow rate and at 8.0 litre min^{-1} (fig. 6), the counter counter flow mode was 220% more efficient than the normal mode.

The heat extracted in a given sample time (200 s) for the double pass counter counter flow mode as a function of water and blood flow rates is shown in figure 7.

TABLE II. *Total heat extracted* (ΣQ) (*kJ*) *for four different patterns of double pass water flow with blood flow rate* 1.27 *litre* min^{-1}; *water flow rate* 2.5 *litre* min^{-1}

	Water flow pattern			
Time (s)	Parallel inner core, parallel outer jacket	Parallel inner core, counter outer jacket	Counter inner core, parallel outer jacket	Counter inner core, counter outer jacket
20	0.01	0.015	0.013	0.016
40	0.02	0.027	0.022	
60	0.032	0.033	0.031	0.046
80	0.042		0.043	0.057
82		0.049		
100	0.05		0.052	0.067
102		0.058		
132	0.059			0.079
152	0.067	0.076	0.069	
184				0.098
190				0.108
202		0.092	0.081	
204	0.081			
242		0.103		
276				0.122

Table III compares the heat extracted for the case of the double and single pass counter counter mode configurations. The data presented in this table have been extracted from figures 4, 5 and 7.

To achieve a water flow rate per channel of 2.5 litre min^{-1} in a double pass system, a water supply of 2.5 litre min^{-1} was required, and this produced a heat extraction of 0.102 kJ (table III). On the other hand, in the single pass configuration for the same channel flow, 2.5 litre min^{-1} was required from two separate sources of supply, but this method would be more efficient with a heat extraction of 0.129 kJ. An

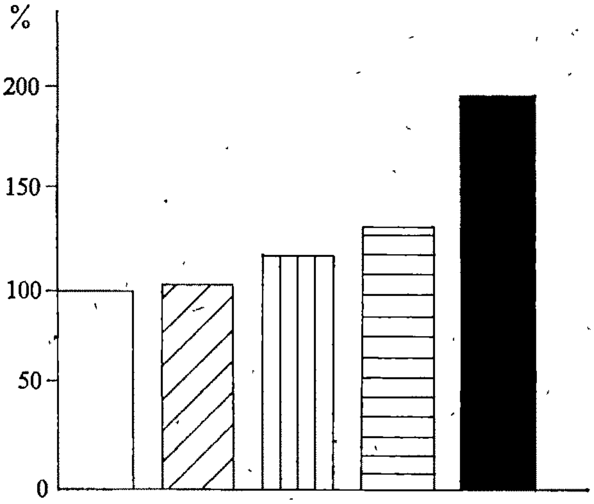

FIG. 5. Relative performance of the different modes of water flow in the heat exchanger, with water flow rate 2.5 litre min^{-1}, blood flow rate 1.27 litre min^{-1}. □ parallel inner core, parallel outer jacket; /// counter inner core, parallel outer jacket; ▥ parallel inner core, counter outer jacket; ▤ counter inner core, counter outer jacket; ■ counter inner core, counter outer, single pass.

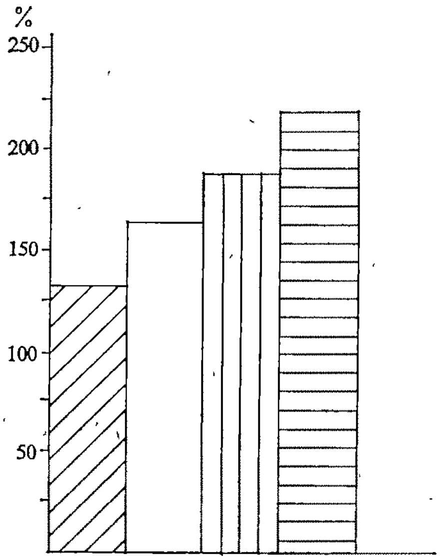

FIG. 6. Relative performance of the double pass counter counter mode compared to the normal mode as a function of water flow rate at a constant blood flow rate of 1.27 litre min^{-1}. *Water flow rate*: /// 2.5 litre min^{-1}; □ 4.5 litre min^{-1}; ▥ 6.0 litre min^{-1}; ▤ 8.0 litre min^{-1}.

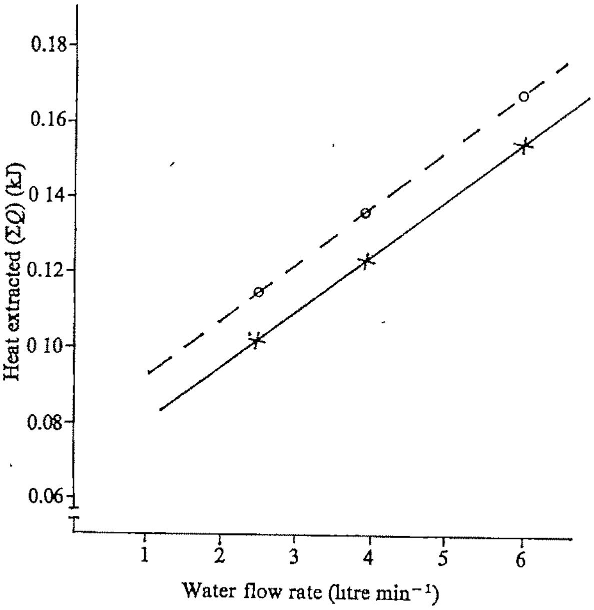

FIG. 7. Heat extracted in the double pass counter counter flow mode as a function of water and blood flow rates. Blood flow rates: ——, 1.27 litre min^{-1}; - - - -, 2.54 litre min^{-1}.

TABLE III. *Heat extracted by the double and single pass counter counter flow mode with a blood flow rate of* 1.27 *litre min*$^{-1}$

Water flow rate per channel (litre min^{-1})	Mode of counterflow pattern	Heat extracted ΣQ (kJ) (200 s)
2.5	Double pass	0.102
2.5	Single pass	0.129
5.0	Double pass	0.139

alternative method of producing 2.5 litre min^{-1} in the single pass mode would be to divide a supply capacity of 5 litre min^{-1}. However, if this 5-litre min^{-1} supply capacity were utilized in the double pass system, then 0.139 kJ of heat would be extracted in comparison with 0.129 kJ (table III).

Figure 8 shows the variation in pressure decrease as a function of water flow rate for the Rygg-Kyvsgaard shell-type heat exchanger used in this series of experiments.

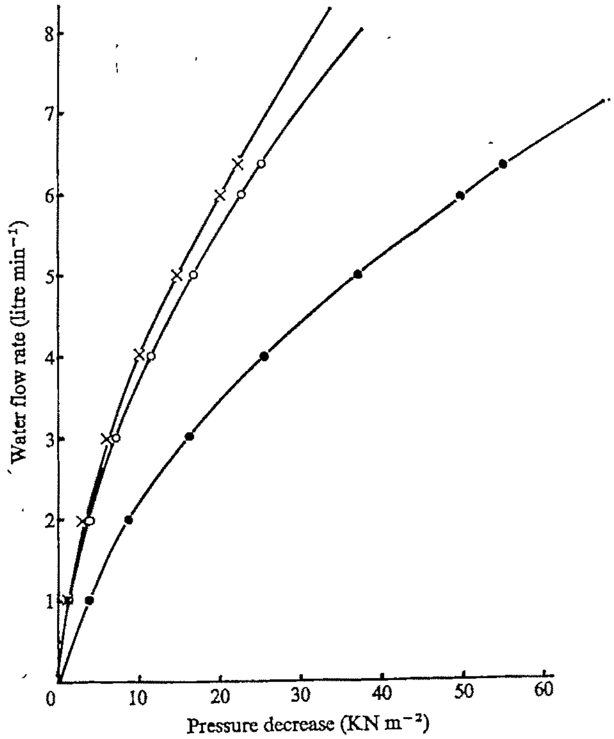

FIG. 8. Distribution of decrease in pressure *v.* water flow rate. ● = total heat exchanger; × = outer jacket; ○ = inner core.

DISCUSSION

With a single, small flow rate supply of water, the most efficient heat transfer is achieved if this flow is utilized in the counter counter double pass mode. However, if a twin water supply is available, then one would obtain an enhanced performance by a single pass counter counter flow configuration.

REFERENCE

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PERFORMANCE D'UN ECHANGEUR DE CHALEUR DU TYPE "EN COQUILLE" POUR LA CIRCULATION EXTRACORPORELLE

RESUME

On a procédé à des essais sur un échangeur de chaleur du type "en coquille" utilisé pour une simulation de circulation extracorporelle. Le mode de contre-courant a été le modèle le plus efficace et dans cet article l'auteur fait des recommandations sur le modèle d'écoulement à utiliser avec les faibles débits d'eau.

EINE LEISTUNGSSTUDIE EINES WÄRMEAUSTAUSCHGERÄTES VOM GEHÄUSETYP BEI ZIRKULATION AUSSERHALB DES KÖRPERS

ZUSAMMENFASSUNG

An einem "Gehäuse"—Wärmeaustauschgerät wurden bei einer simulierten Zirkulation ausserhalb des Korpers Tests durchgeführt. Die Gegenstrom-Betriebsweise erwies sich als die leistungsfähigste, und es wurden Empfehlungen gemacht, welche Durchflussweise bei niedrigen Wasser-Durchflussraten angewendet werden soll.

RENDIMIENTO DE UN TERMOCAMBIADOR DE TIPO TUBULAR PARA CIRCULACION EXTRACORPOREA

SUMARIO

Se realizaron pruebas con un termocambiador de tipo tubular empleado para la circulación extracorpórea simulada. El modo de contracorriente fue el más eficaz y se hacen recomendaciones en virtud de las cuales el tipo de circulación va acompañado por flujos de agua de escasa velocidad.

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PULMONARY MECHANICS DURING GENERAL ANAESTHESIA

The influence of mechanical irritation on the airway

S. DOHI AND M. I. GOLD

SUMMARY

The changes in pulmonary resistance (R_L) and compliance (C_L), following airway irritation and surgical stimulation, were investigated in 19 anaesthetized, paralysed patients. Thirteen were normal, while six had objective evidence of chronic obstructive pulmonary disease (COPD). Broncho–carinal irritation with a suction catheter produced a 27% increase in R_L (0.58 ± 0.32 kPa litre^{-1} s to 0.74 ± 0.40, $P < 0.01$) and a 10% decrease in C_L (0.87 ± 0.19 litre kPa^{-1} to 0.81 ± 0.22, $P < 0.01$). These changes were associated with a significant increase in systolic arterial pressure and heart rate during clinical stages of anaesthesia (end-tidal enflurane, $1.3 \pm 0.4\%$, Pa_{CO_2} 5.20 ± 0.53 kPa). These changes did not correlate with depth of anaesthesia, but all returned to the pre-irritation value within 5 min. There was no difference in subjects considered normal and those with COPD. Surgical stimulation did not produce significant changes in pulmonary mechanics; however, repeated broncho–carinal irritation during surgery was associated with a transient increase in R_L ($P < 0.01$).

Irritation of the laryngeal (Nadel and Widdicombe, 1962a; Tomori and Widdicombe, 1969) and tracheobronchial mucosa (Tomori and Widdicombe, 1969) causes bronchial constriction in paralysed animals. Don and Robson (1966), however, did not observe such changes in the mechanical properties of the total respiratory system in apnoeic, anaesthetized man.

There is an assumption, which is not based on actual measurement of pulmonary mechanics, that bronchoconstriction is induced by airway irritation or surgical stimulation in lightly anaesthetized man (Wylie and Churchill-Davidson, 1972) and especially in those with chronic obstructive pulmonary disease (COPD) (Wylie and Churchill-Davidson, 1972; Bergman, 1976). Shnider and Papper (1961) observed that asthmatic patients had a significantly greater frequency of wheezing following the induction of anaesthesia and tracheal intubation and Simonsson, Jacobs and Nadel (1967) noted that patients with reactive airways disease showed a more intense reaction to minor stimulation than did normal patients. The purpose of our study was to measure and compare the changes in pulmonary mechanics following both tactile stimulation of the airway and a surgical incision in anaesthetized, paralysed normal patients and those with COPD.

METHODS

Nineteen adult male patients (aged 27–81 yr) were studied awake and during general endotracheal anaesthesia. Elective lower abdominal or orthopaedic surgery was performed. Informed consent was obtained from each patient. In six patients, with a history of COPD and of cough and sputum for 3 months or more each year for at least 2 yr (Stuart-Harris et al., 1965), the arterial blood-gas tensions and spirograms were abnormal. Identical criteria enabled us to classify the other 13 patients as being without pulmonary disease. Premedication with morphine 0.1–0.15 mg kg^{-1}, hydroxyzine 1.0–1.4 mg kg^{-1} and atropine 0.4–0.5 mg was administered by i.m. injection 1 h before arrival in the operating room, after which an oesophageal balloon was inserted through the nose under topical anaesthesia and positioned in the middle third of the oesophagus. The balloon tip lay 35–45 cm from the nares and contained 0.2 ml of air (Milic-Emili et al., 1964).

Measurements of transpulmonary pressure (P_T), flow rate ($\dot{V}$) and tidal volume (V_T) were made, with the patient awake and in the supine position, during quiet breathing through a mouthpiece and with a nose-clip in position. Following the administration of tubocurarine 3 mg i.v., anaesthesia was induced with thiopentone 5 mg kg^{-1} i.v. Suxamethonium 100 mg i.v. was administered to facilitate the insertion of an

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endotracheal tube (9.0 mm i.d.). Each subject was given oxygen 6 litre min^{-1} with enflurane via a semiclosed circle carbon dioxide absorption system. Muscle paralysis was maintained with tubocurarine 0.3 mg kg^{-1} and the lungs were ventilated mechanically by an Air Shields or Ohio anaesthesia ventilator with an expired tidal volume of 10–12 ml kg^{-1} and a peak inspiratory flow rate of 30–40 litre min^{-1}. The depth of anaesthesia was regulated according to the patient's clinical status and the adequacy of muscular relaxation was confirmed by the total absence of response to a twitch stimulus. The end-tidal carbon dioxide concentration was maintained at approximately 5% with the use of a Capnograph infra-red analyser (Goddart) calibrated with two concentrations of carbon dioxide (3.82% and 8.05%), and recordings were made on an Omniscribe, A5241–12.

Measurements of P_T, $\dot{V}$ and V_T were made immediately after intubation and these were followed by measurements every 5 min. Twenty-five to 30 min after intubation, an end-tidal gas sample was collected, through a small polyethylene catheter placed within the tracheal tube, for the analysis of its anaesthetic concentration using a gas chromatograph. A polyethylene whistle tip suction catheter (14 f.g.) was inserted to the tracheal tube until the tip was 40 cm from the orifice of the tube. The lower trachea, carina–bronchi were irritated by advancing and retracting the catheter five times within 5 s and the catheter was withdrawn. Measurements were taken immediately after irritation and then every 5 min for 15 min. The measurements were repeated at the start of surgery. Forty-five to 60 min later, broncho–carinal irritation with the suction catheter was repeated, followed by identical measurements.

Average lung resistance (R_L) and lung compliance (C_L) values were calculated from the flow–pressure–volume curves using the isovolumetric technique (Amdur and Mead, 1958; Gold and Helrich, 1965). Gas flow was measured with a Fleisch heated pneumotachograph and a differential pressure transducer (Statham PM5C), and a volume signal was obtained by electrical integration of flow. The pneumotachograph was calibrated with a Fischer–Porter rotameter (MSA 13357) with oxygen; volume was calibrated with a giant syringe (500 and 1000 ml). P_T was measured with a differential transducer (Statham PM 131 TC), the top of which was connected to the oesophageal balloon (P_{ES}) and the bottom to an opening in the side of the endotracheal tube (P_A). R_L and C_L were expressed as the mean value of five consecutive breaths in each series. Values determined in the anaesthetized, intubated subjects were corrected by subtracting the measured resistance to gas flow within the endotracheal tube at corresponding flow rates. Mean flow rates were: awake 0.5 litre s^{-1}; during anaesthesia 0.6 litre s^{-1}; a correction value of 1.1 cm H_2O $litre^{-1}$ s was added to correspond to the resistance of the upper airway (Hyatt and Wilcox, 1961) (this had been excluded from measurement in the intubated anaesthetized subjects). Arterial pressure was measured with a Statham P23 Ia transducer and all variables recorded with an Electronics for Medicine VR-6 carrier–amplifier. Pa_{O_2}, Pa_{CO_2} and pH were determined using Radiometer ABL-1 or BMS 2 MK2 electrodes. The end-tidal concentrations of enflurane were measured with a 402 F & M Packard gas chromatograph. Data were analysed using Student's *t* test for paired data and then for unpaired data in two groups (with or without COPD) and also by covariance analysis. Results are presented as mean (± SD) and a statistically significant change was considered to have occurred when *P* values were 0.05 or less.

RESULTS

Pulmonary mechanics and demographic data are shown in tables I and II. Immediately after intubation, mean R_L increased significantly (10 of 11 normal and four of five COPD subjects) (fig. 1). In 10 patients there were further increases in R_L 5 min after intubation. Thereafter R_L remained stable. Differences in the mean values of R_L immediately and 25–30 min after intubation were not statistically significant.

Following the first broncho–carinal irritation R_L increased (fig. 1) in all patients except two of the normal patients. However, it decreased to the pre-irritation value 5 min later. Changes in R_L following the surgical incision were not significant (fig. 2). There was an increase of R_L following the second period of irritation (45–60 min after incision) (fig. 2). These returned to the pre-irritation value within 5 min. The change in R_L after the first period of irritation was 12% greater than after the second ($P > 0.05$).

Mean C_L decreased immediately after intubation and then increased gradually (fig. 3). Irritation of the lower airway decreased C_L, but a large decrease in C_L was seen only when the increase in R_L was equally large. The surgical incision and the second broncho–carinal irritation were not associated with any statistically significant change (fig. 4).

TABLE I. *Patients without COPD* (R_L = *kPa litre*$^{-1}$ *s*; C_L = *litre kPa*$^{-1}$)

	Age (yr)	Wt (kg)	Ht (cm)	FEV$_1$/FVC (%)	Awake R_L	Awake C_L	Intubation R_L	Intubation C_L	5 min R_L	5 min C_L	25–30 min R_L	25–30 min C_L	Irritation 1 R_L	Irritation 1 C_L	5 min R_L	5 min C_L
	27	73	178	88	0.35	1.37	0.71	0.88	0.73	0.83	0.65	0.96	0.76	0.96	0.57	0.96
	28	57	169	80	0.28	1.73	0.29	0.61	0.33	0.82	0.27	1.19	0.33	1.19	0.30	1.22
	38	73	178	87	0.27	1.41	0.36	1.25	0.28	1.19	0.38	1.04	0.39	0.94	0.39	0.99
	50	60	171	83	0.23	1.57	—	—	0.47	0.66	0.48	0.66	0.76	0.46	0.53	0.40
	52	64	180	81	0.45	1.59	0.54	0.94	0.53	1.17	0.51	1.16	0.97	1.04	0.70	1.11
	53	76	168	82	0.37	0.79	0.40	0.56	0.42	0.70	0.41	0.75	0.44	0.66	0.38	0.69
	54	67	185	79	0.33	1.80	0.48	1.28	0.52	1.53	0.46	1.99	—	—	—	—
	54	67	173	73	0.25	1.09	0.42	0.98	0.42	0.94	0.35	0.92	0.43	0.88	0.39	0.87
	56	90	168	75	0.40	0.80	0.47	0.77	0.49	0.78	0.44	0.74	0.54	0.74	0.49	0.76
	60	99	178	79	0.58	1.03	0.58	0.69	0.54	0.82	0.58	0.82	0.56	0.83	0.48	0.79
	69	77	173	80	0.44	0.74	0.53	0.33	0.54	0.48	0.40	0.73	0.47	0.69	0.42	0.79
	66	71	165	70	0.48	0.71	0.67	0.69	0.70	0.70	0.65	0.61	0.64	0.62	0.63	0.60
	66	84	175	92	0.41	1.45	—	—	0.68	0.77	0.48	1.05	0.64	0.88	0.46	1.00
Mean	52	74	174	80.7	0.37	1.24	0.50**	0.82**	0.50	0.82*	0.47	0.97	0.58*	0.83*	0.48*	0.85
±SD	13.5	11.9	5.7	6.1	0.10	0.40	0.12	0.29	0.13	0.29	0.11	0.36	0.18	0.20	0.11	0.23

	Age (yr)	Wt (kg)	Ht (cm)	FEV$_1$/FVC (%)	Preop. R_L	Preop. C_L	Incision R_L	Incision C_L	5 min R_L	5 min C_L	45–60 min R_L	45–60 min C_L	Irritation 2 R_L	Irritation 2 C_L	5 min R_L	5 min C_L
	27	73	178	88	0.57	0.96	0.69	0.89	0.61	0.94	—	—	—	—	—	—
	28	57	169	80	0.31	1.23	0.33	1.24	0.24	1.31	0.22	1.29	0.28	1.30	0.28	1.29
	38	73	178	87	0.37	0.92	0.35	0.89	0.40	1.04	0.42	0.92	0.42	0.89	0.36	0.94
	50	60	171	83	0.42	0.58	0.46	0.53	0.53	0.40	0.60	0.88	0.64	0.92	0.60	0.90
	52	64	180	81	0.69	1.21	0.68	1.22	0.64	1.10	0.63	0.89	0.67	0.93	0.63	0.92
	53	76	168	82	0.45	0.68	0.40	0.72	0.44	0.67	0.44	0.74	0.54	0.78	0.49	0.64
	54	67	185	79	0.46	1.99	0.36	2.04	0.45	1.78	—	—	—	—	—	—
	54	67	173	73	0.41	0.84	0.36	0.83	0.33	0.81	—	—	—	—	—	—
	56	90	168	75	0.49	0.78	0.51	0.75	0.54	0.78	0.53	0.79	0.58	0.77	0.54	0.77
	60	99	178	79	0.48	0.79	0.55	0.75	0.68	0.74	0.52	0.71	0.81	0.64	0.54	0.72
	69	77	173	80	0.42	0.75	0.39	0.76	0.37	0.74	0.34	0.75	0.37	0.71	0.35	0.73
	66	71	165	70	0.59	0.59	0.63	0.59	0.52	0.59	—	—	—	—	—	—
	66	84	175	92	0.53	0.96	0.54	0.99	0.49	0.90	—	—	—	—	—	—
Mean	52	74	174	80.7	0.48	0.94	0.48	0.94	0.48	0.91	0.46	0.87	0.54	0.87	0.47	0.86
±SD	13.5	11.9	5.7	6.1	0.10	0.37	0.13	0.39	0.12	0.35	0.14	0.19	0.17	0.20	0.12	0.20

* Significant change from previous value ($P < 0.05$).

** Significant change from previous value ($P < 0.01$).

1 cm H_2O = 0.0980638 kPa.

TABLE II. *Patients with COPD* (R_L = *kPa litre*$^{-1}$ *s;* C_L = *litre kPa*$^{-1}$)

	Age (yr)	Wt (kg)	Ht (cm)	FEV_1/FVC (%)	Awake R_L	Awake C_L	Intubation R_L	Intubation C_L	5 min R_L	5 min C_L	25–30 min R_L	25–30 min C_L	Irritation 1 R_L	Irritation 1 C_L	5 min R_L	5 min C_L
	43	67	170	73	0.52	1.13	0.87	0.80	1.21	0.71	0.65	0.75	1.46	0.63	0.68	0.69
	56	42	174	68	0.48	0.73	—	—	0.57	0.66	0.55	0.66	0.61	0.68	0.57	0.68
	62	76	180	64	0.52	1.05	0.88	0.77	0.60	0.90	0.53	1.00	0.63	0.93	0.60	1.00
	70	50	175	47	0.74	0.74	1.51	0.57	2.48	0.88	1.79	1.13	1.95	1.22	1.75	1.08
	79	76	180	69	0.54	1.15	0.56	1.03	0.57	1.00	0.62	0.88	0.68	0.83	0.68	0.84
	81	63	168	59	0.81	0.49	0.77	0.46	0.86	0.60	0.79	0.62	0.94	0.54	0.92	0.54
Mean	65	62	175	63.3	0.60	0.88	0.92	0.72*	1.05	0.79	0.82	0.84	1.04	0.80	0.86	0.80
±SD	14.5	13.9	5.0	9.3	0.14	0.27	0.35	0.22	0.74	0.16	0.49	0.20	0.55	0.25	0.45	0.21

	Age (yr)	Wt (kg)	Ht (cm)	FEV_1/FVC (%)	Preop. R_L	Preop. C_L	Incision R_L	Incision C_L	5 min R_L	5 min C_L	45–60 min R_L	45–60 min C_L	Irritation 2 C_L	Irritation 2 C_L	5 min R_L	5 min C_L
	43	67	170	73	0.73	0.72	0.77	0.71	0.96	0.62	0.84	0.69	1.11	0.62	0.75	0.69
	56	42	174	68	0.57	0.68	0.51	0.67	0.62	0.66	0.60	0.67	0.60	0.66	0.56	0.69
	62	76	180	64	0.62	0.99	0.59	0.96	0.58	0.95	0.57	0.89	0.50	0.94	0.58	0.98
	70	50	175	47	1.74	1.08	1.68	1.05	1.62	1.06	1.79	1.07	1.98	1.08	1.78	1.07
	79	76	180	69	0.69	0.90	0.70	0.90	0.70	0.95	0.69	0.93	0.76	0.95	0.71	0.99
	81	63	168	59	0.88	0.53	—	—	0.90	0.51	0.88	0.45	0.97	0.48	0.99	0.47
Mean	65	62	175	63.3	0.87	0.82	0.85	0.86	0.90	0.79	0.90	0.78	0.99*	0.79	0.89	0.81
±SD	14.5	13.9	5.0	9.3	0.44	0.21	0.47	0.17	0.39	0.22	0.46	0.22	0.54	0.23	0.46	0.24

* Significant change from previous value ($P < 0.05$).

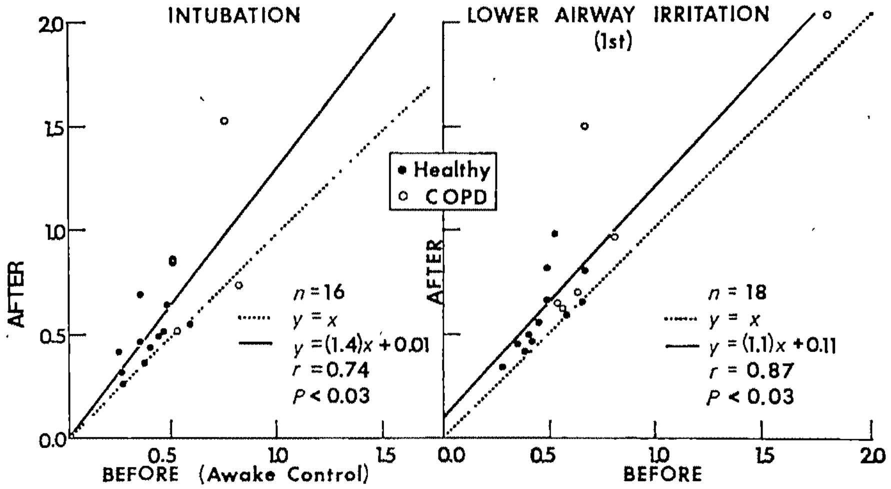

FIG. 1. Change in R_L (kPa litre^{-1} s) before *v.* after intubation (left) and airway stimulation (right) for healthy patients (●) and patients with COPD (○).

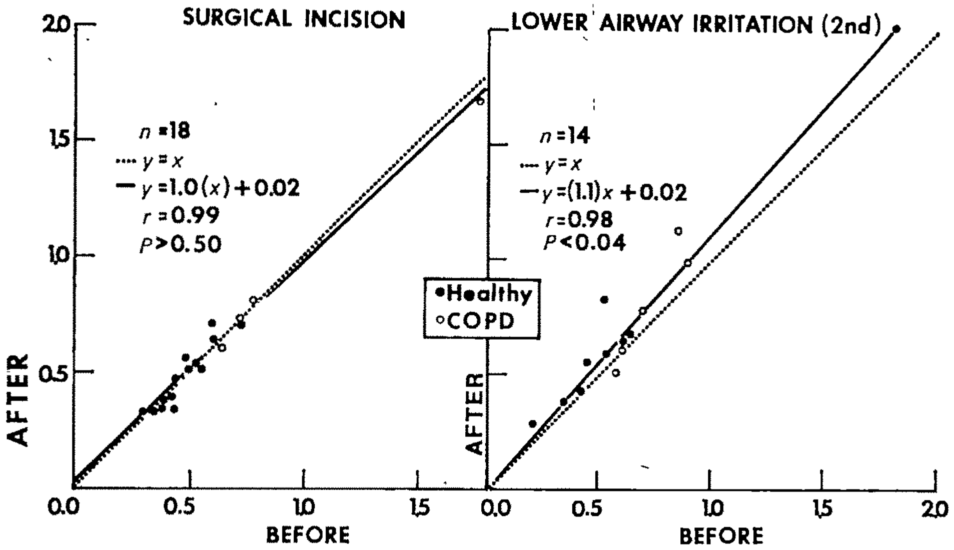

FIG. 2. Effect of surgical incision and second stimulation of airway on R_L (kPa litre^{-1} s) in healthy patients (●) and those with COPD (○).

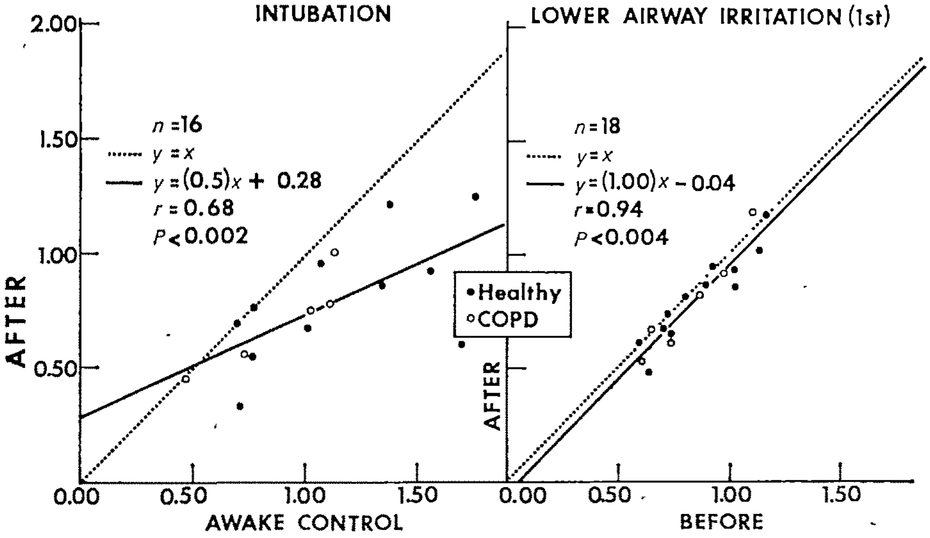

FIG. 3. Change in C_L (ml kPa^{-1}) before *v.* after intubation (left) and airway stimulation (right) for healthy patients (●) and those with COPD (○).

There was no significant difference in those changes in R_L and C_L in normal subjects and those with COPD at any time except for the awake control values (table I). The magnitude of change of R_L at the time of initial lower airway irritation was 0.23 ± 0.29 kPa litre^{-1} s in those with COPD and 0.11 ± 0.14 kPa litre^{-1} s in non-COPD subjects.

The average changes in mean arterial pressure and heart rate are presented in figure 5. All patients showed increases in arterial pressure, C_L and R_L in response to intubation, to irritation of the lower airway and to surgical incision within 1 min after manipulation (fig. 6). End-tidal P_{CO_2} remained constant throughout the study in all subjects after

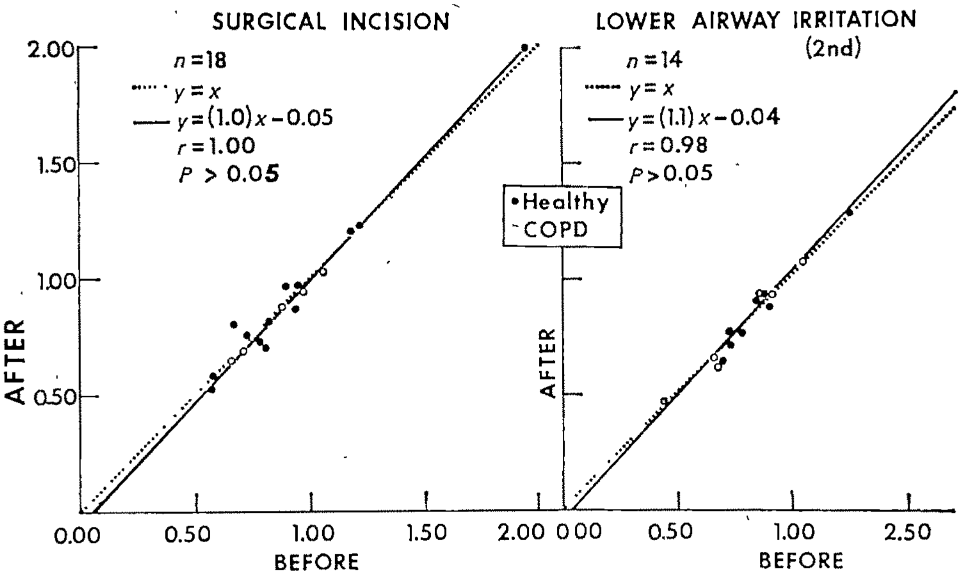

FIG. 4. Effect of surgical incision and second stimulation of airway on C_L (ml kPa^{-1}) in healthy patients (●) and those with COPD (○).

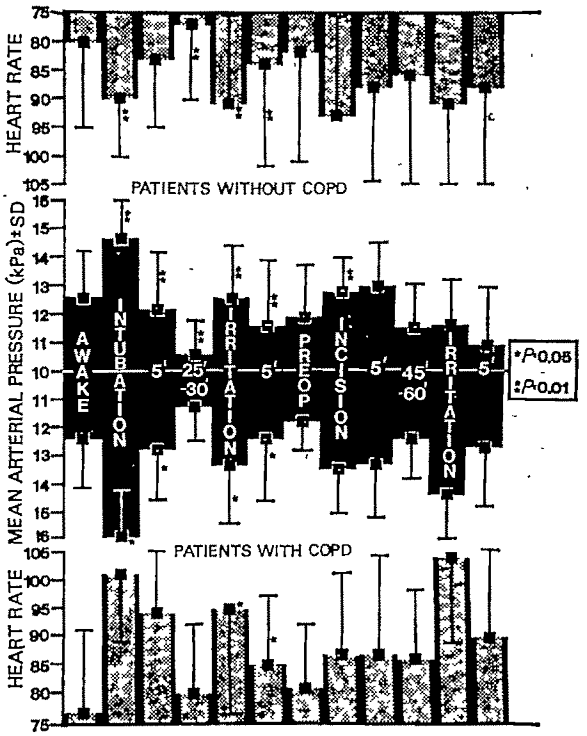

FIG. 5. Mean (and SD) values of heart rate (beat min^{-1}) and mean arterial pressure (kPa) for the two groups studied, at the different stages of the study. * **: significant change from previous value.

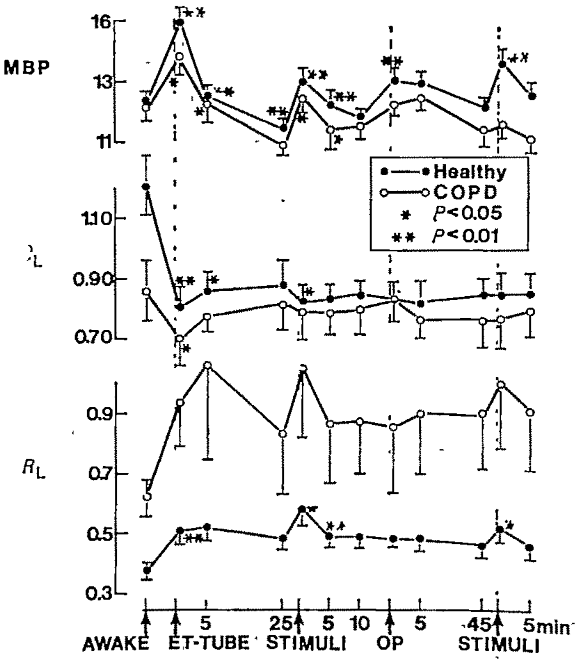

FIG. 6. Mean (and SD) values of mean arterial pressure (MBP) (kPa), compliance (C_L) (ml kPa^{-1}) and resistance R_L (kPa litre^{-1} s) at the different stages of the study. * **: significant change from previous value.

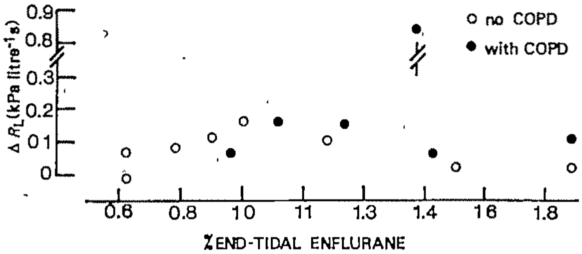

FIG. 7. Relationship between end-tidal enflurane concentration (% v/v) and increase in R_L, 30 min following induction.

initial adjustment of mechanical ventilation. At 25–30 min after the induction of anaesthesia, Pa_{CO_2} in normal subjects was 5.11 ± 0.67 kPa, Pa_{O_2} was 48.93 ± 10.4 kPa and pH was 7.39 ± 0.05 unit; in those with COPD, Pa_{CO_2} was 5.00 ± 0.44 kPa, Pa_{O_2} 44.26 ± 6.93 kPa and pH 7.43 ± 0.06. There was no significant difference between the two groups.

Mean values (± SD) of end-tidal enflurane concentration were 1.4% (± 0.36) in COPD and 1.0% (± 0.32) in normal subjects ($P > 0.05$). There was no correlation between the changes in R_L, arterial pressure and end-tidal enflurane concentrations (fig. 7).

DISCUSSION

This study presents evidence that irritation of the broncho–carinal area and insertion of the endotracheal tube produced a significant increase in R_L and a small decrease in C_L, associated with significant cardiovascular changes. These results were not influenced by other factors known to affect pulmonary mechanics, including hypoxia (Nadel and Widdicombe, 1962b), deep inspiration (Nadel and Tierney, 1961) and changes in respiratory frequency (Cutillo et al., 1973; Hedenstierna and McCarthy, 1975) and in Pa_{CO_2} (Newhouse et al., 1964). Changes in lung volume (Vincent et al., 1970) might have occurred, but the brief time interval (seconds) between irritation and measurement are assumed to have precluded this. The values for R_L both in awake, premedicated and in anaesthetized, paralysed patients in this study agree with those reported previously for awake (Frank, Mead and Ferris, 1957) and for anaesthetized, curarized subjects (Gerbershagen and Bergman, 1967).

Don and Robson (1966) suggested that mechanical irritation of the lower airway in apnoeic anaesthetized man did not result in any significant change in the mechanical properties of the lungs and chest wall. However, failure to demonstrate change following stimulation might have been a result of a transient response which returned to the control value before the first measurement was made. Further, their study did not exclude the effect on R_L of the hyperventilation which was used to reinstitute apnoea (Newhouse et al., 1964). Furthermore, suppression of any reflex effect of lower airway irritation with topically administered local anaesthesia (Dain, Boushey and Gold, 1975) was not excluded. Nadel and Widdicombe (1962a) demonstrated that mechanical irritation of the larynx in paralysed cats produced an increase in R_L which returned to control within 1 min. In our study, the increase in R_L at the time of broncho–carinal irritation returned also towards pre-irritation values within 5 min. The decrease in C_L was small and transient also. Therefore, it is likely that bronchial secretions including mucus were not a causal factor in the changes and that reflex bronchoconstriction had occurred (Nadel and Widdicombe, 1962a; Tomori and Widdicombe, 1969). "Cough receptors" are present at the tracheal bifurcation and the area of bronchial branching (Widdicombe and Sterling, 1970). The increase in R_L with tracheal intubation is probably related to the same mechanism although quantitative and qualitative differences in response at different sites in the airway have been reported (Tomori and Widdicombe, 1969). In addition, drugs such as morphine, thiopentone or suxamethonium might have influenced the increase in R_L immediately after intubation. In 11 patients, 5 min later there was a further increase in R_L even though arterial pressure and heart rate had decreased significantly. This might have been a result of a light level of anaesthesia, all patients having received tubocurarine before this. Although Gerbershagen and Bergman (1967) do not consider that R_L is influenced by tubocurarine it may have had an effect on these patients (Crago et al., 1972).

Surgical stimulation was associated with an increase in arterial pressure and heart rate, but did not affect R_L; it may decrease C_L (Bromage, 1958), but C_L remained stable before and after the beginning of surgery in our study. The small, but significant increase in R_L corresponded to the second broncho–carinal irritation, which produced a smaller change in R_L than the first and no significant decrease in C_L, and may be partly the result of release of catecholamines, secondary to increased sympathetic nervous system activity. Stimulation of the respiratory tract affects systemic arterial pressure and heart rate in paralysed cats (Nadel and Widdicombe, 1962a; Tomori and Widdicombe, 1969) and following tracheotomy in man (Corbett, Kerr and Prys-Roberts, 1968).

The airway response in this investigation did not correlate with the depth of anaesthesia. Failure of the suppressive effect of general anaesthesia on reflex bronchoconstriction may relate to the relatively light plane of anaesthesia in spite of morphine and hydroxyzine premedication. To avoid "bucking" after tracheal intubation the recommendation to administer at least 1.5 MAC has been made (Yakaitis, Blitt and Angiulo, 1977). In Guedel's classification, as described by Gillespie (1943), plane III or IV of stage III anaesthesia with diethyl ether are required to depress laryngeal and cough reflexes. However, Hickey and associates (1969) found no change in R_L (spontaneous, not evoked) in the dog when the halothane concentration was increased from 0.5 (maximal effect) to 2.4 MAC. They showed that halothane progressively inhibited the response of the bronchi to vagal stimulation and this effect was maximal and complete at approximately 0.6 MAC.

In the six patients with COPD, broncho-carinal stimulation increased R_L but there was no statistically significant difference in responsiveness to airway irritation between these and the normal subjects, although the former are considered to have a lower threshold to airway stimulation (Simonsson, Jacobs and Nadel, 1967). The reasons for the failure to induce changes are not clear. There were only six patients with COPD, and there was a relatively wide variation of anaesthetic concentration and distinct individual variations in the increase in R_L. Even among normal, awake subjects there seems to be a wide individual variation of airway response to histamine administered i.v. (Laitinen et al., 1976). Further, it may be that the intensity of stimulation was not applied identically to the same site in the broncho-carinal area in all patients.

Brakensiek and Bergman (1970) suggested that the beneficial effect of halothane in both preventing and treating episodes of bronchospasm was related to the anaesthetic action of halothane in blocking the reflex responses to stimuli which elicit bronchospasm in susceptible individuals. Klide and Aviado (1967) attributed this to beta-adrenergic stimulation. The present study with enflurane suggests that the reflex bronchoconstriction associated with increases in arterial pressure and heart rate following airway irritation occurs during general anaesthesia both in normal subjects and in those with COPD. The increased pulmonary resistance is of short duration and usually too small to be of clinical significance. This transient, small change in R_L may be attributed to the depressant effect of enflurane.

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MECANIQUE DES POUMONS PENDANT UNE ANESTHESIE GENERALE

Influence de l'irritation mecanique sur les passages d'air

RESUME

Les changements se produisant dans la résistance pulmonaire (R_L) et la compliance pulmonaire (C_L) á la suite d'une irritation des passages d'air et de la stimulation chirurgicale, ont été observés sur 19 patients paralysés, anesthésiés. Treize ont été trouvés normaux, alors que six d'entre eux montraient des preuves évidentes d'une maladie chronique d'obstruction pulmonaire (COPD). L'irritation broncho-carénée á l'aide d'un cathéter aspirateur a donné une augmentation de 27% de la R_L (qui est passée de 0,58 ± 0,32 à 0,74 ± 0,40 kPa litre^{-1}, $P < 0,01$), de même qu'une diminution de 10% de la C_L (celle-ci passant de 0,87 ± 0,19 à 0,81 ± 0,22 litre kPa^{-1}, $P < 0,01$). Ces changements ont été associés à une augmentation significative de la pression artérielle systolique et de la fréquence cardiaque pendant les stades cliniques de l'anesthésie (enflurane à la fin du volume courant 1,3 ± 0,4%, Pa_{CO_2} 5,20 ± 0,53 kPa). Ces changements n'ont pas été en corrélation avec la profondeur de l'anesthésie, mais tous sont retournés dans les 5 min á la valeur qui existait avant l'irritation. Il n'y a eu aucune différence entre les sujets considérés normaux et ceux atteints de COPD. La stimulation chirurgicale n'a produit aucun changement significatif dans la mécanique des poumons; cependant une irritation broncho-carénée répétée pendant l'intervention chirurgicale a été associée á une augmentation transitoire de la R_L ($P < 0,01$).

PULMONARTECHNIK WÄHREND EINER VOLLNARKOSE

Die wirkung mechanischer reize auf die luftwege

ZUSAMMENFASSUNG

In 19 anästhesierten, paralysierten Patienten wurden die Veränderungen im pulmonarischen Widerstand (R_L) und in der Lungenausdehung (C_L) durch Reizung der Luftwege und chirurgische Anreizungen untersucht. Sechs Patienten hatten objektive Anzeichen eines chronisch-obstruktiven Lungenleidens (COPD), und 13 waren normal. Bronchokarinaler Anreiz mit einem Saugkatheter erreichte eine 27%ige Vergrösserung des pulmonarischen Widerstandes (0,58 ± 0,32 kPa liter^{-1} s bis auf 0,74 ± 0,40, $P < 0,01$) und eine 10%ige Verminderung der Lungenausdehnung (0,87 ± 0,19 bis auf 0,81 ± 0,22 Liter kPa^{-1}, $P < 0,01$). Diese Veränderungen wurden mit einem bedeutend, erhöhten systolisch-arteriellen Druck und Herzschlag während der klinischen Phasen der Narkose (end-tidales Enfluran 1,3 ± 0,4%, Pa_{CO_2} 5,20 ± 0,53 kPa) in Verbindung gebracht. Diese Veränderungen standen nicht mit der Tiefe der Narkose in Wechselbeziehungen, aber alle kehrten innerhalb von 5 Min zu den Vorreizwerten zurück. Es gab keinen Unterschied zwischen den als normal angesehenen Patienten und denen mit COPD. Chirurgische Anreizung produzierte nur unbedeutende Veränderungen im Lungenmechanismus, jedoch wurde wiederholte bronchokarinale Anreizung während der chirurgischen Behandlung mit einer flüchtigen Vergrösserung des R_L in Zusammenhang gebracht ($P < 0,01$).

MECANICA PULMONAR DURANTE ANESTESIA GENERAL

La influencia que ejerce la irritación mecánica sobre la vía respiratoria

SUMARIO

Se investigaron los cambios en la resistencia pulmonar (R_L) y en la elasticidad pulmonar (C_L), tras producirse una irritación y estímulo quirúrgico en las vías respiratorias de 19 pacientes anestesiados, paralizados. Trece se comportaron normalmente, mientras que seis presentaron evidencia objetiva de una enfermedad pulmonar obstructiva crónica (COPD). La irritación broncocarinal producida con una sonda de aspiración dio como resultado un aumento

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A NEW METHOD FOR MEASURING $P\text{CO}_2$ DURING ANAESTHESIA

D. Z. N. Frankel, G. Sandham and A. S. Rebuck

SUMMARY

We have evaluated a new method for measuring the oxygenated mixed venous $P\text{CO}_2$ ($P\bar{v}_{\text{CO}_2}$) in patients undergoing general anaesthesia. The lungs were inflated with a gas mixture containing 0% carbon dioxide and then 12% carbon dioxide and the expired gas was analysed both before and after a brief period of breath-holding. $P\bar{v}_{\text{CO}_2}$ was estimated from the differences in carbon dioxide concentration before and after the apnoeic period. Simultaneous measurements of Pa_{CO_2} were made in blood obtained from radial artery puncture. The range of Pa_{CO_2} studied was 3.2–6.13 kPa. The relationship between mixed venous and arterial $P\text{CO}_2$ was found to be $Pa_{\text{CO}_2} = 0.87\ P\bar{v}_{\text{CO}_2} - 0.44$ ($r = 0.91$). We conclude that this method for measuring $P\bar{v}_{\text{CO}_2}$ can be used during anaesthesia allowing Pa_{CO_2} to be estimated with considerable accuracy.

Attempts have been made to measure $P\text{CO}_2$ of mixed venous blood ($P\bar{v}_{\text{CO}_2}$) with a rebreathing technique (Campbell and Howell, 1962), but despite its elegance and accuracy this method is not used widely in anaesthesia, presumably because many clinicians prefer to have extra information which is provided by arterial blood sampling ($P\text{O}_2$ and pH).

As the level of arterial oxygenation can now be measured non-invasively and without delay using fibreoptic ear oximetry (Saunders, Powles and Rebuck, 1976), a non-invasive method for measuring $P\text{CO}_2$ in blood would be valuable. We have studied the changes in $P\text{CO}_2$ that occurred when alveolar gas was equilibrated with mixed venous blood during a short period of breath-holding (Frankel, Mahutte and Rebuck, 1978).

In healthy subjects, in patients with lung disease and in patients in respiratory failure undergoing artificial ventilation, we compared our breath-holding technique based on this principle with Campbell and Howell's rebreathing method of deriving $P\bar{v}_{\text{CO}_2}$. There was an excellent correlation between $P\bar{v}_{\text{CO}_2}$ derived by breath-holding and direct $P\bar{v}_{\text{CO}_2}$ measurements obtained using a pulmonary artery catheter ($r = 0.97$). From $P\bar{v}_{\text{CO}_2}$ we were able also to estimate arterial $P\text{CO}_2$ with accuracy ($r = 0.96$). We now report a series of studies of this method in anaesthetized patients over a wide range of $P\text{CO}_2$. Our findings suggest that a non-invasive breath-holding method for measuring mixed venous $P\text{CO}_2$ during anaesthesia is feasible, and could prove to be useful when repeated measurements of $P\text{CO}_2$ are required and where arterial puncture is undesirable.

METHODS

Principle of the method

During breath-holding, alveolar $P\text{CO}_2$ increases at a gradually decreasing rate. The carbon dioxide partial pressure approaches asymptotically that of oxygenated mixed venous blood. These changes have been described mathematically by Chilton and Stacy (1952) and DuBois, Britt and Fenn (1952), whose equations are based on the principles that the rate of output of carbon dioxide into the lung is proportional to the arterio–venous content difference and cardiac output, and that the consequent change in $P\text{A}_{\text{CO}_2}$ is inversely proportional to the size of the reservoir into which the carbon dioxide is delivered.

Thus, for the first 15 s of breath-holding:

$$P\text{A}_{\text{CO}_2\,(t)} = P\bar{v}_{\text{CO}_2} - (P\bar{v}_{\text{CO}_2} - P\text{A}_{\text{CO}_2\,(t-0)})e^{-Kt} \qquad (1)$$

where K is a constant and equals $\dot{Q}S(B-47)/\text{ELV}$, $\dot{Q}$ = pulmonary blood flow, S = slope of the oxygenated carbon dioxide dissociation curve, B is the barometric pressure, ELV is the "equivalent lung volume" for carbon dioxide (the carbon dioxide capacity of the lung tissue, blood and alveolar gas), $P\text{A}_{\text{CO}_2\,(t)}$ is the alveolar $P\text{CO}_2$ at time t, which is measured from the end of the inspiration of the test gas mixture. DuBois, Britt and Fenn (1952) and Defares (1958) have confirmed experimentally that the equation described accurately the time course of alveolar

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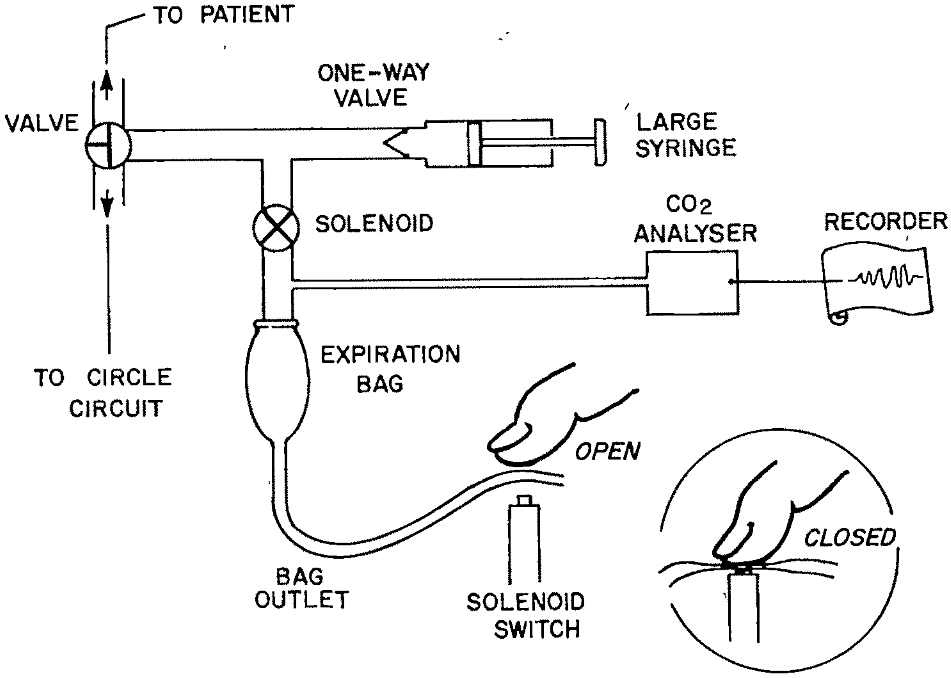

FIG. 1. Circuit diagram for measuring $P\bar{v}_{CO_2}$ during anaesthesia. When the solenoid valve is closed, 1 litre of gas is delivered from the large syringe. Expiration is initiated by depressing the solenoid switch, allowing 500 ml of gas to flow into the 500-ml expiration bag.

P_{CO_2} during breath-holding. We have used this equation to calculate $P\bar{v}_{CO_2}$ by measuring changes in alveolar P_{CO_2} during breath-holding. Pa_{CO_2} was estimated by multiplying $P\bar{v}_{CO_2}$ by 0.8 (McEvoy, Jones and Campbell, 1974).

The experimental circuit for measuring $P\bar{v}_{CO_2}$ used in the present study is shown in figure 1. A large syringe was used to deliver the inspiratory volume of 1000 ml; this syringe was connected in parallel to a solenoid which was used to ensure that gas was exhaled only at predetermined times. P_{CO_2} was measured distal to the solenoid valve using a Godart MKII Capnograph calibrated for use with nitrous oxide (Kennell, Andrews and Wollman, 1973) and recorded on a Hewlett-Packard Model 7101B recorder. The distal end of the exhalation bag was fitted with a rubber tube which was occluded between thumb and solenoid switch during exhalation. At the end of expiration, when the solenoid was closed, the rubber tube from the exhalation bag was open to allow rapid equilibration with ambient pressure and ensure rapid emptying.

$P\bar{v}_{CO_2}$ was measured as follows. At the end of expiration, the lungs were inflated with 1000 ml of 60% nitrous oxide in oxygen. After 5 s, 500 ml was expired passively into the 500-ml expiration bag. After a 10-s breath-holding period, a further 500 ml was expired. The procedure was repeated with a mixture of 12% carbon dioxide and 60% nitrous oxide in oxygen and $P\bar{v}_{CO_2}$ was calculated from the exponential changes in $P_{A_{CO_2}}$. An essential feature of this approach is that it is unnecessary to make any calculations utilizing exponential functions. As the decay and rise curves for the high and low carbon dioxide mixtures are derived under identical conditions, e^{-Kt} is constant and is replaced by a single value.

Example of calculation of $P\bar{v}_{CO_2}$ from the four data points

From figure 2—when carbon dioxide-free gas was inhaled—the 5- and 15-s $P_{A_{CO_2}}$ values (corrected for 60% nitrous oxide) were 2.8% (1) and 4.6% (2) respectively. When 12% carbon dioxide was inhaled, the 5- and 15-s $P_{A_{CO_2}}$ values were 7.5% (3) and 6.7% (4) respectively. As 10 s of breath-holding elapsed

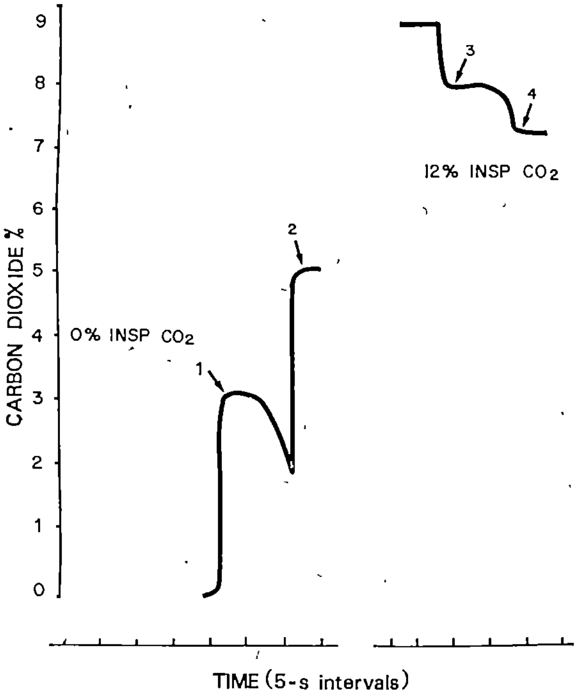

FIG. 2. Expired carbon dioxide record during the four periods of breath-holding (uncorrected for nitrous oxide). In the lower left trace when the inspired carbon dioxide was 0%, the two expirations at 5 and 15 s were 3.2 and 5.1% respectively. The notations 3 and 4 in the right trace, represent carbon dioxide values after inhaling 12% carbon dioxide in oxygen.

between the two alveolar samples, equation (1) becomes

$$P\text{A}_{\text{CO}_2(15)} = P\bar{\text{v}}_{\text{CO}_2} - (P\bar{\text{v}}_{\text{CO}_2} - P\text{A}_{\text{CO}_2(5)})\text{e}^{-10K}$$

Substituting:

$$\text{For } 12\%\text{:}\quad 6.7 = P\bar{\text{v}}_{\text{CO}_2} - (P\bar{\text{v}}_{\text{CO}_2} - 7.5)\text{e}^{-10K}$$

$$\text{For } 0\%\text{:}\quad 4.6 = P\bar{\text{v}}_{\text{CO}_2} - (P\bar{\text{v}}_{\text{CO}_2} - 2.8)\text{e}^{-10K}$$

(Only the final per cent value need be converted to $P\text{CO}_2$ by multiplying × P_B).

For each breath-hold period, K remains the same and constant, so that e^{-10K} is a constant. By subtraction, $\text{e}^{-10K} = 2.1/4.7 = 0.45$ and by substitution in either equation, $P\bar{\text{v}}_{\text{CO}_2} = 6.0\%$ or 5.73 kPa ($P_B = 101.33$ kPa).

PROCEDURE

Six healthy ASA Class I or II patients, three males and three females, aged 34–67 yr (mean = 53) undergoing thoracic surgical procedures (oesophageal repair, one; hiatus hernia repair, five), were studied. Informed consent was given by all the patients.

Anaesthesia was induced with thiopentone 3–5 mg kg^{-1} and endotracheal intubation was performed following the administration of pancuronium 0.1 mg kg^{-1}. The lungs were ventilated with a mixture of 60% nitrous oxide in oxygen using a circle system with fresh gas flows and minute ventilation calculated to give a normal $P\text{a}_{\text{CO}_2}$ (DeSilva, 1976). Morphine i.v. and supplementary pancuronium were given as required. The patients were positioned in the right lateral position and surgery commenced. Arterial blood for gas analysis was sampled via a radial artery catheter which had been inserted percutaneously. The lungs were ventilated at eucapnic values for 30 min and $P\bar{\text{v}}_{\text{CO}_2}$ and $P\text{a}_{\text{CO}_2}$ were measured.

To induce a rapid decrease in $P\text{a}_{\text{CO}_2}$ of 2–2.67 kPa, the inspired $P\text{CO}_2$ was decreased by increasing fresh gas flows and turning the carbon dioxide absorber into the circuit (DeSilva, 1976). The rapid changes in $P\text{a}_{\text{CO}_2}$ and $P\bar{\text{v}}_{\text{CO}_2}$ were measured every 5 min for 20 min (Nunn, 1960). Inspired $P\text{CO}_2$ was increased subsequently by turning the carbon dioxide absorber out of the circuit, and returning fresh gas flows to the original settings. $P\text{a}_{\text{CO}_2}$ and $P\bar{\text{v}}_{\text{CO}_2}$ were measured every 5 min for 20 min.

RESULTS

The range of $P\text{a}_{\text{CO}_2}$ values studied was 3.2–6.13 kPa. There was a good correlation between arterial $P\text{CO}_2$ and $P\bar{\text{v}}_{\text{CO}_2}$ as illustrated in figure 3 ($P\text{a}_{\text{CO}_2} = 0.87$

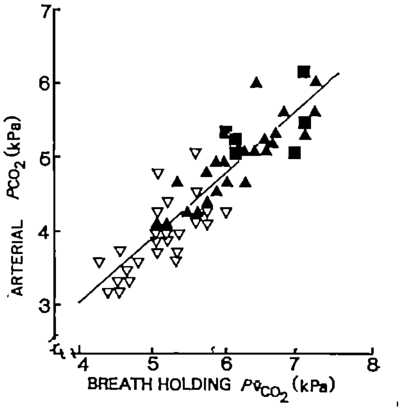

FIG. 3. Measured arterial $P\text{CO}_2$ plotted against $P\bar{\text{v}}\text{CO}_2$ obtained by breath-holding, derived from 54 studies in six patients: $P\text{a}_{\text{CO}_2} = 0.87\ P\bar{\text{v}}_{\text{CO}_2} - 0.44$ ($r = 0.91$). ■ = initial $P\text{CO}_2$ in each patient; ▽ = values obtained during progressive hypocapnia; ▼ = values obtained as $P\text{CO}_2$ was allowed to increase towards initial values.

$P\bar{v}_{CO_2} - 0.44$, $r = 0.91$). The mean difference between estimated ($0.8\,P\bar{v}_{CO_2}$) and measured Pa_{CO_2} was 0.047 kPa (SD = 0.33). The difference between predicted and measured Pa_{CO_2} was not significantly different during steady-state, increasing, or decreasing PCO_2 ($P = 0.05$).

In all patients, heart rate and arterial pressure remained within ±20% of the initial values throughout the test periods.

The measurements did not interfere with any surgical procedure, and there were no untoward patient reactions.

DISCUSSION

The present study has shown that arterial PCO_2 can be determined reliably from the oxygenated mixed venous PCO_2 obtained by breath-holding during anaesthesia. We have used this method successfully in patients undergoing thoracic surgery under conditions of steady-state and rapidly changing inspired carbon dioxide; there is a good correlation with the arterial PCO_2 measured directly. These results confirm that the relationship between mixed venous and arterial PCO_2 (McEvoy, Jones and Campbell, 1974) can be expressed as $Pa_{CO_2} = 0.8\ P\bar{v}_{CO_2}$ during a steady or changing state during anaesthesia.

We have used an equation based on several reasonable assumptions to derive $P\bar{v}_{CO_2}$ from the experimental data. These assumptions were: (1) that PA_{CO_2} is equal to pulmonary end-capillary PCO_2; (2) that the carbon dioxide dissociation curve is virtually linear within the experimental range; (3) that cardiac output remains constant during breath-holding (Hong et al., 1971); (4) that lung volume remains virtually unchanged during 10 s of breath-holding (Mithoefer, 1959); (5) that the inspired gas mixture is distributed evenly throughout the lungs. Although this last assumption is unlikely to be valid in patients with lung disease, the assumption seems reasonable because breath-holding may increase gas mixing in poorly ventilated areas (Buist and Ross, 1974). Hence, it is likely that variations in these variables would make only small differences to the calculated values of $P\bar{v}_{CO_2}$.

The non-invasive measurement of PCO_2 by the breath-holding technique offers several advantages over other methods. End-tidal PCO_2 is influenced by both arterial PCO_2 and alveolar deadspace. With increasing deadspace, end-tidal PCO_2 will decrease even in the face of unchanged or increasing arterial PCO_2 (Hackney, Sears and Collier, 1958). The breath-holding method, however, is not influenced by changing deadspace and directly reflects Pa_{CO_2} values. Skin carbon dioxide sensors, although non-invasive, are still in the developmental stages and the relationship between skin PCO_2 and arterial PCO_2 is unclear especially during shock states. Even in healthy subjects, there is a 15-min time lag between step changes in Pa_{CO_2} and transcutaneous PCO_2 equilibration (Severinghaus, 1978).

Rebreathing techniques for measuring $P\bar{v}_{CO_2}$ require careful manipulation of the initial bag PCO_2, in an attempt to obtain an equilibrium between mixed venous blood, lung and rebreathing bag PCO_2 (Jones and Rebuck, 1973). During anaesthesia, the addition of nitrous oxide with its effects on the measurement of carbon dioxide by infra-red analysis would complicate further the manipulation of the initial bag PCO_2. By contrast, our suggested breath-holding technique uses standard mixtures of carbon dioxide for all patients. In addition, the nitrous oxide concentration is unchanged during the procedure and thus a correction factor is applied easily to the measurement of carbon dioxide.

The patients in this study were healthy and did not have pre-existing lung disease. However, in our previous study (Frankel, Mahutte and Rebuck, 1978), we have shown that the breath-holding method gives reproducible and accurate results in patients with lung disease breathing spontaneously or being ventilated artificially via an endotracheal tube.

We derived the same arterial/mixed venous PCO_2 relationship during surgery, as others have obtained in the awake state, even though surgery and anaesthesia may have profound effects on the arterio–venous PCO_2 difference. Anaesthesia reduces carbon dioxide production (Nunn, 1960), while positive pressure ventilation tends to decrease cardiac output. Thoracic surgery in the lateral position with an open chest and manipulation of the lung disturbs the normal ventilation–perfusion relationships. Despite these various potential influences on the arterial/mixed venous PCO_2 relationship (Powles and Campbell, 1978), we obtained an excellent correlation between Pa_{CO_2} calculated from expired gas and Pa_{CO_2} obtained directly. It seems, therefore, that these potentially disturbing influences were either small or mutually compensatory.

Previously it was accepted widely that arterial PCO_2 was under most circumstances 0.8 kPa less than $P\bar{v}_{CO_2}$. The equation $Pa_{CO_2} = 0.8\ P\bar{v}_{CO_2}$ describes the relationship more accurately and was described recently by McEvoy, Jones and Campbell (1974).

They discussed several factors which might influence the venoarterial $P\text{CO}_2$ difference, but did not speculate on the unique nature of its mathematical relationship. According to the Fick equation:

$$C\bar{v}_{\text{CO}_2} - Ca_{\text{CO}_2} = \dot{V}\text{CO}_2/\dot{Q}$$

where $C\bar{v}_{\text{CO}_2}$ and Ca_{CO_2} are the carbon dioxide contents of mixed venous and arterial blood respectively, $\dot{V}\text{CO}_2$ is the rate of production of carbon dioxide and $\dot{Q}$ is the cardiac output. Thus, the mixed venous–arterial carbon dioxide content difference remains the same independent of the value of $P\text{CO}_2$, as long as $\dot{V}\text{CO}_2$ and cardiac output remain constant. The results in the present study lead us to conclude that the $Pa_{\text{CO}_2}/P\bar{v}_{\text{CO}_2}$ fraction also remains constant at 0.8, even at different values of $P\text{CO}_2$.

The present study has extended our previous report (Frankel, Mahutte and Rebuck, 1978) in which we described our breath-holding method for measuring $P\text{CO}_2$ in conscious volunteers and patients with lung disease. The method described in the present report is a simple, non-invasive test for measuring mixed venous $P\text{CO}_2$ during anaesthesia. It may be used in changing or steady-states of $P\text{CO}_2$. Arterial $P\text{CO}_2$ may be estimated by multiplying $P\bar{v}_{\text{CO}_2}$ by 0.8. We suggest that the method offers several advantages over other available techniques for assessing the adequacy of alveolar ventilation and provides an alternative to direct arterial puncture.

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NOUVELLE METHODE POUR MESURER LA P_{CO_2} PENDANT L'ANESTHESIE

RESUME

Nous avons procédé à l'évaluation d'une nouvelle méthode permettant de mesurer la $P\text{CO}_2$ veineuse mélangée et oxygénée ($P\bar{v}_{\text{CO}_2}$) sur des malades soumis à une anesthésie générale. On a gonflé les poumons à l'aide d'un mélange de gaz contenant 0% de gaz carbonique et ensuite 12% de gaz carbonique, puis analysé le gaz expiré avant et après une bréve retenue de la respiration. La $P\bar{v}_{\text{CO}_2}$ a été estimée à partir des différences dans la concentration de gaz carbonique avant et après la période d'apnée. Des mesures simultanées de la Pa_{CO_2} ont été prises dans le sang obtenu par la perforation de l'artère radiale. La plage des Pa_{CO_2} étudiées a été de 3,2–6,13 kPa. La relation entre la $P\text{CO}_2$ veineuse mélangée et la $P\text{CO}_2$ artérielle que l'on a trouvée, a été $Pa_{\text{CO}_2} = 0{,}87P\bar{v}_{\text{CO}_2} - 0{,}44$ ($r = 0{,}91$). Nous en concluons que cette méthode de mesure de la $P\bar{v}_{\text{CO}_2}$ peut être utilisée pendant une anesthésie, ce qui permet d'estimer la Pa_{CO_2} avec une très grande précision.

EINE NEUE METHODE, KOHLENDIOXYDSPANNUNG WÄHREND DER NARKOSE ZU MESSEN

ZUSAMMENFASSUNG

Wir haben für Patienten, die eine Vollnarkose erhielten, eine neue Methode ausgewertet, um die Sauerstoff angereicherte, gemischt-venöse Kohlendioxydspannung ($P\bar{v}_{CO_2}$) zu messen. Die Lungen wurden mit einer Gasmischung von 0% Kohlendioxyd und dann 12% Kohlendioxyd angefullt und das ausgeatmete Gas wurde vor und nach einem kurzen Atemanhalten analysiert. Die $P\bar{v}_{CO_2}$ wurde aus den Unterschieden in der Kohlendioxydkonzentration vor und nach der Atemstockung errechnet. Zur gleichen Zeit wurde die arterielle Kohlendioxydspannung (Pa_{CO_2}) gemessen in Blut, das direkt von der Pulsader durch Einstich gewonnen worden war. Der studierte Bereich der arteriellen Kohlendioxydspannung (Pa_{CO_2}) reichte von 3,2–6,13 kPa. Das Verhältnis zwischen gemischtem venösen und arteriellen P_{CO_2} war $Pa_{CO_2} = 0{,}87 P\bar{v}_{CO_2}$ minus 0,44 ($r = 0{,}91$). Wir schliessen daraus, dass diese Methode, $P\bar{v}_{CO_2}$ zu messen, während einer Anästhesie benutzt werden kann, um Pa_{CO_2} mit beträchtlicher Genauigkeit festzustellen.

UN METODO NUEVO PARA MEDIR EL $P\mathrm{co}_2$ DURANTE LA ANESTESIA

SUMARIO

Hemos evaluado un nuevo método para medir el $P\mathrm{co}_2$ ($P\bar{v}_{CO_2}$) venoso mezclado oxigenado en pacientes sometidos a anestesia general. Los pulmones fueron inflados con una mezcla de gas que contenía un 0% de dioxido de carbono y luego un 12% de dioxido de carbono, analizándose el gas expirado, tanto antes como después de un período breve en que se retuvo la respiración. El $P\bar{v}_{CO_2}$ se calculó a base de la diferencia entre las concentraciones previa y posterior al período apneico. Se tomaron mediciones simultáneas del Pa_{CO_2} en la sangre obtenida mediante punción de arteria radial. La variación de Pa_{CO_2} que se estudió fue de 3,2–6,13 kPa. La relación entre el $P\mathrm{co}_2$ venoso mezclado y el arterial se descubrió era $Pa_{CO_2} = 0{,}87\ P\bar{v}_{CO_2} - 0{,}44$ ($r = 0{,}91$). Concluimos que este metodo de medir el $P\bar{v}_{CO_2}$ puede emplearse durante la anestesia, permitiendo que el Pa_{CO} sea calculado con considerable precisión.

Br. J. Anaesth. (1979), **51**, 221

ATROPINE REVERSAL OF HYPERCARBIA DURING ENFLURANE ANAESTHESIA

W. M. WAHBA AND J. SADKOVA

SUMMARY

Atropine was given i.v. to 35 spontaneously breathing healthy adults anaesthetized with enflurane to determine if it would reduce Pa_{CO_2} by improving gas exchange. Five minutes after administration of atropine, Pa_{CO_2} decreased from mean 7.18 to 6.65 kPa (−7%), while mean $\dot{V}_E$ increased from 4.8 to 6.1 litre min^{-1} (+27%). These changes were maintained 15 min later in the 20 patients studied at that time. Older and more obese patients showed a more significant change. Respiratory frequency and Pa_{O_2} did not alter.

During a study of the pattern of breathing during enflurane anaesthesia, we found that there was a relationship between the forced expiratory volume in one second ($FEV_{1 \cdot 0}$) and Pa_{CO_2}. The increase in Pa_{CO_2} during anaesthesia compared with the value before anaesthesia correlated with the ratio $FEV_{1 \cdot 0}$/vital capacity* while the values during anaesthesia correlated with the ratio $FEV_{1 \cdot 0}$/height.† We suggested that airway resistance (R_{AW}) may influence the increase in Pa_{CO_2} occurring under general anaesthesia with spontaneous ventilation. If this is so, a reduction in R_{AW} should improve pulmonary ventilation. The present study was designed to test this hypothesis by measuring expired minute volumes ($\dot{V}_E$) and arterial blood-gas tensions before and after the i.v. administration of atropine in 35 healthy adult patients undergoing minor peripheral surgery. Atropine was chosen because its effects on flow resistance have been measured by Don and Robson (1965).

METHODS

Thirty-five healthy adults undergoing elective operations on the periphery of the body gave consent for the study, which was approved by the Hospital Research and Ethics Committee. Measurements were made in all patients (group I) 5 min after the injection of atropine and in 20 (group II) the measurements were repeated 20 min after injection. The 15 patients in group I who were studied only at 5 min were not distinctly different from the other patients. The biometric data are summarized in table I.

Premedication consisted of anileridine (U.S.P.) 12.5–37.5 mg and promethazine 12.5–25 mg, according to body weight, given i.m. 1 h before operation. After induction of anaesthesia with thiopentone 2–3 mg kg^{-1} i.v. and orotracheal intubation facilitated by suxamethonium 1 mg kg^{-1}, all the subjects received enflurane in nitrous oxide 3 litre min^{-1} and oxygen 2 litre min^{-1} from a semi-closed circle system with carbon dioxide absorption. Ventilation was assisted manually until the patient resumed adequate spontaneous breathing. The vaporizer (Cyprane) setting of 2–3% was adjusted on the basis of arterial pressure, heart rate, lack of lacrimation and the absence of response to surgical stimulation. No change in the vaporizer setting was made during the period of study. Twenty to 30 min after the surgical incision was made, when tidal volume and frequency were steady for 5 min, $\dot{V}_E$ was measured using a Wright respirometer connected to a low resistance, uni-directional valve. Tidal volume (V_T) was derived from the measured values of $\dot{V}_E$ and breathing frequency (f). The measured values were not corrected to BTPS. Arterial blood was obtained from a radial artery anaerobically into heparinized syringes, which were packed in ice. Blood-gas tensions and pH were determined within 10 min using standard electrodes calibrated with 0, 5 and 10% carbon dioxide (Corning 165 blood-gas analyser). The results were not corrected for time, introducing a

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* ΔPa_{CO_2} (kPa) = 10.08 − 0.08 $FEV_{1 \cdot 0}$/VC ($r = 0.6$ $P < 0.01$).

† Pa_{CO_2} (kPa) = 9.17 − 1.2 $FEV_{1 \cdot 0}$/height (m) ($r = 0.65$ $P < 0.001$).

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TABLE I. *Details of patients studied (mean ± SEM)*

Group	Basis of classification	Age (yr)	Weight (kg)	Height (cm)	Weight/Height	Surface area* (m^2)
I	Measurements at 5 min only ($n = 35$)	40.1 2.9	70.2 3.2	167.5 2.3	0.42 0.01	1.79 0.03
II	Measurements at 5 and 20 min ($n = 20$)	41.3 4.1	71.6 5.8	169.9 2.2	0.43 0.01	1.80 0.05

* Dubois and Dubois (1916).

possible error of 0.07–0.01 kPa for Pa_{CO_2} (Kelman and Nunn, 1966).

Atropine 0.01 mg kg^{-1} was injected i.v. and the measurements repeated 5 min later in all patients, and 20 min after the injection in 20 patients.

Statistical analysis of the data was performed using Student's *t* test, two-way analysis of variance and by regression analysis using the least squares method.

RESULTS

There were no significant differences between the two groups with respect to age and body build (table I) or in the blood-gas and ventilation values before the administration of atropine (table II). Ventilation before atropine in the 15 patients studied at 5 min was slightly greater than that in the other 20 patients ($P < 0.1$) but there was no significant difference in Pa_{CO_2}.

Five minutes after the injection of atropine, mean $\dot{V}_E$ increased by 27% from 4.8 ± 0.18 to 6.1 ± 0.24 litre min^{-1} in group I ($P < 0.001$). In group II, mean $\dot{V}_E$ also increased by 27% from 4.49 ± 0.21 to 5.69 ± 0.28 litre min ($P < 0.001$). Arterial Pa_{CO_2} in group I decreased by 7% from 7.18 ± 0.16 to 6.65 ± 0.19 kPa ($P < 0.001$). In group II, mean Pa_{CO_2} before atropine was 6.91 ± 0.17 kPa and mean Pa_{CO_2} 5 min after atropine was 6.17 ± 0.20 ($P < 0.001$).

The measurements at 5 min in group II were maintained at 20 min (table II) without any significant difference between the values at these time intervals. For analysis of these data, two-way analysis of variance and Student's *t* test were used.

Respiratory frequency, Pa_{O_2}, pH and standard bicarbonate did not change significantly at any time in either group.

The values of $\dot{V}_E$ were standardized to allow for differences in size between individuals by the use of

TABLE II. *Measurements of ventilation and arterial blood-gases before and after atropine (mean ± SEM)*

Measurement		Group I ($n = 35$) Before	Group I 5 min after	Group I P	Group II ($n = 20$) Before	Group II 5 min after	Group II P	Group II 20 min after	Group II P
Pa_{O_2}	(kPa)	19.16 0.8	19.06 0.67	n.s.	19.61 1.09	19.57 1.08	n.s.	18.96 1.04	n.s.
HCO_3^-	(mmol $litre^{-1}$)	22.6 0.4	20.7 0.4	n.s.	22.2 0.5	22.0 0.6	n.s.	21.4 0.6	n.s.
pH	(unit)	7.25 0.01	7.26 0.01	n.s.	7.24 0.02	7.24 0.08	n.s.	7.26 0.02	n.s.
Pa_{CO_2}	(kPa)	7.18 0.16	6.65 0.19	<0.001	6.91 0.17	6.17 0.20	<0.001	6.33 0.21	<0.001
f	(b.p.m.)	16.0 0.8	16.9 0.8	n.s.	15.9 0.8	16.9 0.7	n.s.	16.8 0.7	n.s.
V_T	(ml)	316.9 15.2	374.2 17.4	<0.001	295.0 18.2	339.0 25.0	<0.001	350.0 20.0	<0.001
$\dot{V}_E$	(litre min^{-1})	4.8 0.18	6.1 0.24	<0.001	4.49 0.21	5.69 0.28	<0.001	5.81 0.35	<0.001
$\dot{V}_E$/SA	(litre min^{-1} m^{-2})	2.66 0.10	3.39 0.13	<0.001	2.46 0.10	3.13 0.15	<0.001	3.21 0.16	<0.001

the ratio $\dot{V}\text{E}$/surface area (SA). Mean $\dot{V}\text{E}$/SA for all subjects increased from 2.66 ± 0.1 to 3.39 ± 0.13 litre $\text{min}^{-1}\,\text{m}^{-2}$ 5 min after atropine ($P<0.001$). In group II patients, $\dot{V}\text{E}$/SA increased from 2.46 ± 0.10 to 3.13 ± 0.15 litre $\text{min}^{-1}\,\text{m}^{-2}$ ($P<0.001$), at 5 min, a value not significantly different from that noted at 20 min (3.21 ± 0.16 litre $\text{min}^{-1}\,\text{m}^{-2}$). Figure 1 shows the observed mean values of Pa_{CO_2} and $\dot{V}\text{E}$/SA in the two groups at the stated time intervals.

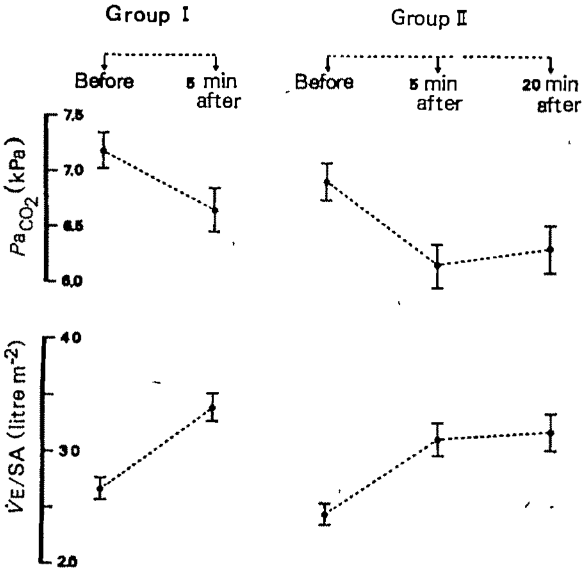

FIG. 1. Changes in mean Pa_{CO_2} and $\dot{V}\text{E}$/SA before and after administration of atropine.

The relationship between $\dot{V}\text{E}$/SA and Pa_{CO_2} for all the data is shown in figure 2. This relationship is expressed by the following equation:

$$Pa_{\text{CO}_2} = 8.5 - 0.61\ \dot{V}\text{E/SA} \quad (r = 0.51,\ P<0.001)$$

DISCUSSION

The anaesthetic technique used in this study may be criticized because alveolar concentrations of the anaesthetic agents were not identical. However, we believe that it is preferable to use the standard technique appropriate for the surgery.

The purpose of the present study was to determine if the i.v. injection of atropine during enflurane anaesthesia would have beneficial effects on gas exchange. Although there were individual differences in the degree of change in Pa_{CO_2} in our patients, mean Pa_{CO_2} decreased and mean ventilation increased markedly following the injection of atropine. These changes may result from a reduction in airway resistance or central stimulation of ventilation.

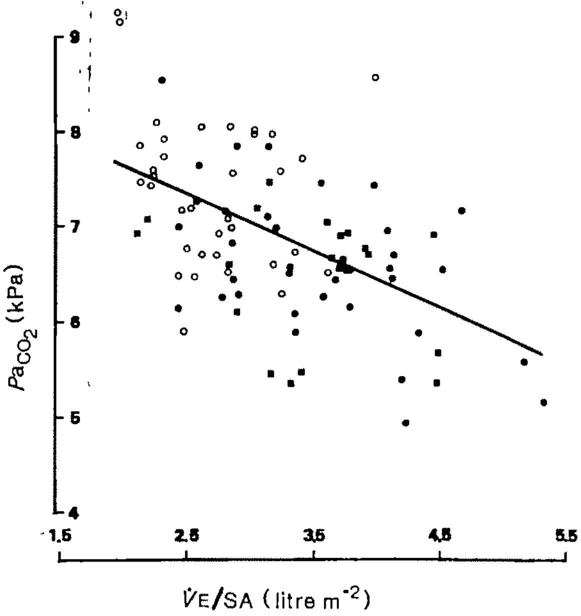

FIG. 2. Relationship between $\dot{V}\text{E}$/SA and Pa_{CO_2} for all measurements. There is a trend with reference to time of sampling. ○ = before atropine; ● = 5 min after atropine; ■ = 20 min after atropine.

Central stimulation would cause an increase in respiratory rate or tidal volume, or both. We found no change in respiratory frequency, but the effect may have been masked by narcotic premedication. An increase in central respiratory drive can be measured by comparing the tracheal pressures generated during airway occlusion (Po) at functional residual capacity (FRC) before and after atropine. These measurements would differentiate between changes in central inspiratory drive and peripheral effects (Milic-Emili and Grunstein, 1976). We performed these measurements in four other subjects (G. B. Drummond and W. M. Wahba, unpublished observations) premedicated with diazepam and anaesthetized with enflurane in a mixture of nitrous oxide in oxygen and found no changes in occlusion pressure or in the ratio of inspiration to expiration. Frequency was unchanged also.

These preliminary results suggest that the main site of action of i.v. atropine is peripheral rather than central. Mean flow rates must have increased following the injection of atropine, probably as a result of reduced airway resistance. There are conflicting reports on the effects of atropine on R_{AW} during anaesthesia. Don and Robson (1965) reported that total flow resistance in patients anaesthetized with nitrous oxide was decreased by 33% following atropine in the same dosage as was used in our study. On the other hand, Brakensiek and Bergman (1970) reported that atropine 0.8 mg i.v. during halothane anaesthesia reduced R_{AW} only in subjects with pre-existing high airways resistance. In awake subjects, R_{AW} is reduced markedly by atropine (Vincent et al., 1970). These authors found that total pulmonary resistance during both inflation and deflation was reduced, with a greater effect during inflation. They confirmed also that lung volume history influences resistance. Daly, Ross and Behnke (1963) reported a small reduction in R_{AW} following atropine in awake man. Groto, Whitman and Arakawa (1978) have reported recently that i.v. atropine 0.008 mg kg^{-1} significantly increased expiratory flow functions ($FEV_{1\cdot0}\%$, maximum mid-expiratory flow and maximum expiratory flow at 50% total lung capacity) with a small, transient and insignificant decrease in R_{AW}. The authors interpreted these observations in six awake volunteers as a decrease in small airways resistance. The improvement in expiratory flow functions was detectable 10 min after injection and lasted longer than 1 h. Thus the bulk of evidence supports the thesis that our results may be explained on the basis of a reduction in R_{AW}.

The increase in tidal volume noted here is greater and of longer duration than that following the insertion and the subsequent removal of resistances (threshold and tubular) in the breathing circuit reported by Nunn and Ezi-Ashi (1961). Vagally mediated respiratory reflexes were probably operative in Nunn's study despite the use of anticholinergic drugs, and this may explain the differences in the results between the two studies.

The lack of a relationship between $\dot{V}_E$/SA and Pa_{CO_2} with time of measurement (fig. 2) is a reflection of individual variability in the change in Pa_{CO_2} and in deadspace, and of the non-steady state. Analysis of individual data at 5 min revealed that the extent of change in Pa_{CO_2} could be related to the age and body build of the patient. By arbitrarily choosing a change in Pa_{CO_2} greater or less than 0.67 kPa, we subdivided our subjects into two groups (table III). The patients with greater reductions in Pa_{CO_2} (mean change of −0.97 kPa) were older and more obese ($P < 0.05$). These patients showed a greater increase in $\dot{V}_E$/SA ($P < 0.01$) and a greater decrease in Pa_{CO_2} ($P < 0.001$) after atropine. It is known that the reduction in FRC following the induction of anaesthesia is greater in older subjects (Hewlett et al., 1974) and also in patients with high weight : height ratios (Don et al., 1970). An inverse relationship exists between lung volume and airway resistance. Greater improvements following atropine may be expected in patients with smaller FRC values where airways resistance has a more marked influence on ventilation. However, obese patients received a larger dose of atropine, since dosage was based on body weight. If this increase in dose was inappropriate, the changes may be a reflection of a dose–response relationship.

Changes in $\dot{V}_E$ precede those in Pa_{CO_2} because of the size of the body stores of carbon dioxide. Consequently, the disproportionate increase in $\dot{V}_E$ (+27%) compared with the decrease in Pa_{CO_2} (−7%) may indicate that a steady state was not present 5 min after injection of atropine. Fifteen minutes later a more clearly defined difference in the distribution of the data relative to the time of measurement could be noted (fig. 3). However, the reduction in Pa_{CO_2} may have been limited by the increasing deadspace and the deepening of anaesthesia. By inference, a steady state was probably absent at 20 min.

TABLE III. *Data grouped for patients who exhibited a change in* Pa_{CO_2} *greater or less than 0.67 kPa following i.v. atropine*

			$\dot{V}_E$/SA (ml m^{-2})		Pa_{CO_2} (kPa)	
	Age (yr)	Wt./ht. (kg cm^{-1})	Before	After	Before	After
Change < 0.67 kPa	35.7	0.40	2.76	3.33	7.2	6.84
	3.4	0.01	0.24	0.28	0.21	0.21
Change > 0.67 kPa	48.5	0.44	2.61	3.39	7.22	6.21
	5.1	0.02	0.10	0.14	0.27	0.33
P	< 0.05	< 0.05	n.s.	< 0.01	n.s.	< 0.001

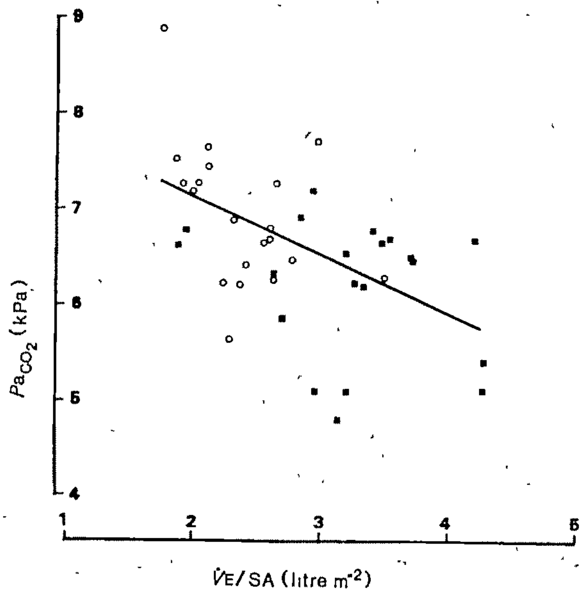

FIG. 3. Relationship between $\dot{V}_E$/SA and Pa_{CO_2} before and 20 min after atropine (group II). There is a distinct trend with reference to time of sampling. ○ = before; ■ = 20 min after.

Hypercarbia causes bronchodilatation (Aviado, 1975) and it is surprising that atropine can still exert such an effect under these circumstances.

The clinical implications of this study are that hypercarbia during enflurane anaesthesia can be limited but not reversed by the use of atropine, particularly in older and more obese patients.

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INVERSION DE L'HYPERCARBIE PAR L'ATROPINE PENDANT UNE ANESTHESIE A L'ENFLURANE

RESUME

On a administré de l'atropine par voie intraveineuse à 35 adultes en bonne santé, respirant spontanément, anesthésiés à l'aide d'enflurane, pour voir si l'on pourrait réduire la Pa_{CO_2} en améliorant l'échange de gaz. Cinq minutes après l'administration d'atropine, la Pa_{CO_2} a diminué d'une moyenne de 7,18 à 6,65 kPa (−7%), alors que le $\dot{V}_E$ moyen a augmenté de 4,8 à 6,1 litre min^{-1} (+27%). Ces variations existaient toujours 15 min plus tard sur les 20 patients qui faisaient à ce moment-là l'objet de l'étude. Les patients plus âgés et plus obèses ont accusé des variations plus prononcées. La fréquence respiratoire et la Pa_{O_2} n'ont pas été modifiées.

DURCH ATROPIN BEWIRKTE AUFHEBUNG VON HYPERKARBIE WÄHREND ENFLURAN-NARKOSE

ZUSAMMENFASSUNG

Atropin wurde intravenös an 35 spontan atmende, gesunde Erwachsene verabreicht, die mit Enfluran narkotisiert waren; es sollte festgestellt werden, ob dies durch verbesserten Gasaustausch zu einer Verringerung von Pa_{CO_2} führen würde. Fünf Minuten nach Verabreichung der Droge sank Pa_{CO_2} von einem Mittelwert von 7,18 auf 6,65 kPa (−7%), während der Mittelwert von $\dot{V}_E$ von 4,8 auf 6,1 Liter min^{-1} (+ 27%) anstieg. Diese Veränderungen blieben erhalten bei den 20 Patienten, die 15 Min später untersucht wurden. Ältere und fettleibigere Patienten zeigten stärkere Veränderungen. Respirationsrate und Pa_{O_2} veränderten sich nicht.

INVERSION POR ATROPINA DE HIPERCAPNIA DURANTE ANESTESIA DE ENFLURANO

SUMARIO

Se administró atropina intravenosamente a 35 adultos saludables anestesiados con enflurano que respiraban espontáneamente, a fin de determinar si se reduciría el Pa_{CO_2} mediante el mejoramiento del intercambio de gas. Cinco minutos después de la administración de atropina, el Pa_{CO_2} disminuyó de un promedio de 7,18 a 6,65 kPa (−7%), mientras que el $\dot{V}_E$ aumentó de 4,8 a 6,1 litros min^{-1} (+27%). Estos cambios continuaban 15 min más tarde en los 20 pacientes estudiados en esa oportunidad. Los pacientes de más edad y más obesos acusaron un cambio más significativo. La frecuencia el Pa_{O_2} no variaron.

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CYCLOPROPANE AND CAESAREAN SECTION

M. B. KRISTOFFERSEN

SUMMARY

In a prospective study 589 patients were anaesthetized by the inhalation of cyclopropane 40% for 2–3 min. Relaxation was provided with suxamethonium and anaesthesia was maintained with cyclopropane 7.5%. The series was divided into four groups: patients in optimal condition (96 elective (group 1), 164 emergency (group 3)) and those not in optimal condition (75 elective (group 2), 254 emergency (group 4)). All infants from groups 1 and 3 had high Apgar scores, and all survived. Infants in groups 2 and 4 had lower Apgar scores, eight and 96 respectively were depressed, and 10 and 20 died because of obstetric and neonatal factors unrelated to the anaesthesia. Respiratory distress syndrome (RDS) developed in 44 infants. Among 29 infants in whom the birth weight was less than 2.5 kg the mortality was 31%, whereas no death occurred in mature infants. RDS was significantly more frequent after elective than after emergency surgery. Neonatal depression was independent of the length of the induction–delivery interval, which averaged 13.3 min. The frequency of awareness was 1.5%.

Although solutions to the major problems associated with general anaesthesia for Caesarean section have been found (Crawford, 1977), disagreement exists still as to the choice of anaesthetic. The ideal agent should be acceptable to the patient, without specific toxicity and without influence on uterine contractility. It should not cause neonatal depression at birth or have any effect upon the postnatal course. The agent should produce sufficient analgesia, prevent awareness and not inconvenience the surgeon.

Cyclopropane has a long and honoured service in obstetric anaesthesia because a high percentage of oxygen can be administered, control of the depth of anaesthesia is achieved readily and, in contrast to practically all other agents, cyclopropane is excreted almost completely via the lungs. Therefore it seemed reasonable to investigate the use of this agent, when administered by a modified technique, for Caesarean section.

The results of a prospective investigation performed during the period April 1972 to March 1976 are reported.

PATIENTS AND METHODS

During the period of the study, 683 Caesarean sections performed in the University Maternity Hospital, Aarhus, Denmark, resulted in 696 infants. The Caesarean section rate was 3.5% of all deliveries and of this total 181 were performed as elective, planned procedures (26.5%), and 502 as emergencies (73.5%). Cyclopropane was administered by a standard technique to 589 patients (86.2%). In 94 patients (13.8%) other techniques were used.

In order to differentiate between anaesthetic and obstetric depression of the neonate, the following criteria were used to identify the optimal cases. The neonate should have a birth weight of greater than 2.5 kg and be without life-threatening congenital malformations, and the indications for Caesarean section should not include obstetric or maternal conditions which may influence the status of the infant at birth. According to these criteria, the series was divided into the groups listed in table I, which shows also the indications for Caesarean section.

Anaesthetic techniques

No premedication was given. All patients received mist. magnesium trisilicate (BPC) 15 ml orally within 30 min of the start of anaesthesia. Lateral tilt was used during transport and on the operating table.

Initially, an i.v. infusion was instituted and atropine 0.6 mg and tubocurarine 3 mg were given i.v. Anaesthesia was induced by the inhalation of cyclopropane 750 ml min^{-1} and oxygen 1 litre min^{-1} for 3 min administered by a to-and-fro system with a Waters canister. Suxamethonium 100 mg was then given i.v., and the trachea was intubated without previous ventilation. Anaesthesia was maintained with cyclopropane 75 ml min^{-1} and oxygen 1 litre min^{-1}. An infusion of suxamethonium and manual normoventilation were continued until delivery, after which anaesthesia was maintained with cyclopropane 20–25% and continuous

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TABLE I. *Optimal and non-optimal conditions and the indications for Caesarean section. (Figures in parentheses show the number of infants in the individual groups)*

Indications for Caesarean section	Cyclopropane						
	Optimal cases		Non-optimal cases		Other techniques		
	Elective	Emergency	Elective	Emergency	Elective	Emergency	Total
Previous LUSCS	40	18			3	3	64
Previous CS—classical	7	3					10
Previous hysterotomy	9	3					12
Disproportion	5	25			2	7	39
Malpresentation	5	9				4	18
Breech presentation	20	18			1	4	43
Uterine inertia		82				7	89
Neurological diseases	3				3	3	9
Local gynaecological conditions	7	6					13
Diabetes mellitus			26	17		1	44
Rhesus immunization			11	5		1	17
Placenta praevia			4	38	1	2	45
Premature separation of placenta				25		8	33
Placenta insufficiency			28	12			0
Intra-uterine asphyxia				131		16	147
Prolapsed cord				2		17	19
Pre-eclampsia–eclampsia				11		11	22
Newborn ⩽ 2500 g							
Malformations			6	13			19
Total	96 (96)	164 (166)	75 (78)	254 (261)	10 (10)	84 (85)	683 (696)

relaxation was obtained with suxamethonium i.v. At the end of the anaesthesia, most of the patients received pethidine 25 mg and chlorpromazine 5 mg i.v.

Clinical assessment

The time from start of anaesthesia to the completion of the delivery was recorded to the nearest minute (I–D interval). Clinical assessment of the infant was made by the Apgar score at 1, 5 and 10 min after complete delivery and from the time to sustained respiration (TSR) which was measured in seconds from the delivery to regular breathing. Neonatal depression was considered present, when the infant had an Apgar-minus-colour score at 1 min ($A-C_1$) of less than 7, a $A-C_5$ less than 8 or a TSR of 60 s or more (Crawford, 1972).

The progress of all neonates was followed until discharge from hospital or death and, if the latter, an autopsy was performed. The cause of death, determined from the clinical findings and the result of the autopsy, was noted.

Each patient was interviewed on the day after operation with special reference to awareness during and dreaming after the operation. The patient's subjective assessment of the anaesthesia was recorded.

RESULTS

The neonate

There were few depressed neonates in the two optimal groups, whereas the two non-optimal groups, and especially the emergency group, included some neonates who were still depressed 10 min after delivery (table II). The frequency of depression in the neonate relative to the I–D interval is presented in figure 1 and showed no increase except that the frequency of depression increased with I-D intervals greater than 18 min. However, the numbers were small and were not statistically significant.

RDS was the most common cause of death in the neonatal period. Premature separation of the placenta and lethal malformations were predominant causes of mortality among the stillborn (table III). Of the neonates, 44 had RDS (table IV), 29 less than and 15 greater than a birth weight of 2.5 kg. RDS was nine times as common among neonates below this weight limit, and deaths occurred only in this group. Divided according to contributory factors (table V),

TABLE II. *Summary of neonatal behaviour*

Group	No. of infants	$A-C_1$	$A-C_5$	$A-C_{10}$	TSR ≥60 s	Neonatally depressed No.	Neonatally depressed %	RDS No.	RDS %	RDS mortality (No.)	Stillborn	Neonatal deaths
Optimal elective	96	7.92	8	8	3	3	3.1	5	5.2	0	0	0
Optimal emergency	166	7.87	7.99	8	6	7	4.2	0	0	0	0	0
Non-optimal elective	78	7.69	7.95	7.99	6	8	10.4	10	12.8	4	1	7
Non-optimal emergency	261	6.86	7.77	7.94	72	96	38.6	24	9.6	5	12	8
Other techniques elective	10	7.80	8	8	1	1	10.0	0	0	0	0	0
Other techniques emergency	85	6.11	7.26	7.81	34	42	57.3	5	5.9	0	12	1

TABLE III. *Infant mortality*

Stillborn ($n = 25$)	
Premature separation of placenta	11
Lethal malformations	6
Complications of diabetes mellitus	2
Rhesus immunization	1
Eclampsia	1
Prolapsed cord	1
Placenta praevia	1
Compound presentation	1
Conjoined twins	1
Neonatal deaths ($n = 16$)	
Hydrops fetalis	2
Sequelae of intra-uterine asphyxia	2
Malformation—died 5 days old	1
Malformations—died 14 and 16 days old	2
Respiratory distress syndrome	9
Total	41

TABLE IV. *Frequency of respiratory distress syndrome*

Birth weight (kg)	Liveborn	RDS	RDS mortality (% of liveborn)	RDS mortality (% of RDS)
<1.0	2	0	0	0
1.0–1.5	17	7 (41.2%)	5 (29.4%)	71.4%
1.5–2.0	43	15 (34.9%)	3 (6.9%)	20.0%
2.0–2.5	56	7 (12.5%)	1 (1.8%)	14.2%
All <2.5	118	29 (24.6%)	9 (7.6%)	31.0%
All >2.5	551	15 (2.7%)	0	0

TABLE V. *Respiratory distress syndrome: contributory factors. (Figure in parentheses show the number of deaths)*

	Birth weight >2.5 kg	Birth weight <2.5 kg
Diabetes mellitus	5	4 (1)
Placenta insufficiency	0	5 (2)
Pre-eclampsia–eclampsia	0	5 (0)
Placenta praevia	1	8 (4)
Intra-uterine asphyxia	4	2 (0)
Premature separation of placenta	0	2 (1)
No special pathology	5	3 (1)

TABLE VI. *The occurrence of awareness*

	Remarks	No. of patients	%
Awareness and pain	1 addicted to morphine 2 intubation difficulties	3	0.5
Awareness, no pain	1 intubation difficulties 1 "convulsions"	6	1
Subliminal awareness	Dreams the night after anaesthesia Dizzy memories	6	1

deaths occurred almost exclusively when Caesarean section was indicated by factors predisposing to RDS, such as diabetes mellitus and placenta praevia.

RDS did not occur following emergency section, in patients whose condition was optimal, whereas five

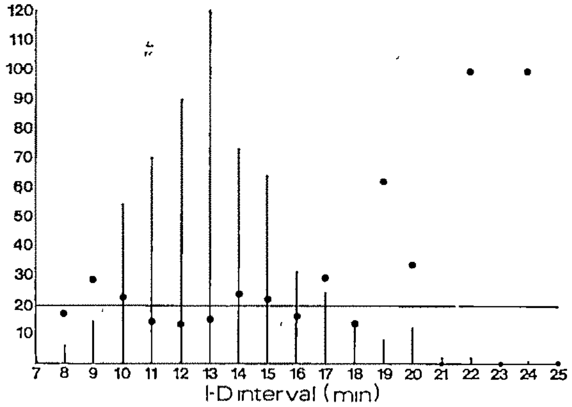

FIG. 1. The relation between neonatal depression and I–D interval. Vertical lines = number of patients at different times; ● = percentages of neonatal depression at different times; horizontal line at 19.4 = average percentage of neonatal depression.

infants from the optimal patients who underwent elective section developed RDS (table II). This difference was statistically significant at the 2.5% level. The frequency of morbidity and mortality caused by RDS in the non-optimal, elective group was 12.9 and 5%, respectively, and contrasted with 9.6 and 2% in the non-optimal, emergency group, which, in fact, comprised a larger number of depressed infants.

The mother

Table VI shows the occurrence of awareness. I–D interval in patients with awareness averaged 13.4 min and ranged from 10 to 16 min. Within the group of patients anaesthetized with techniques other than the cyclopropane method, awareness associated with pain occurred twice. Both occurred in a group of six patients anaesthetized with thiopentone–nitrous oxide–suxamethonium without further supplementation.

Most of the patients were satisfied with the anaesthesia, and no accidents related to cyclopropane occurred. Generally, the mean arterial pressure was increased (20–40 mm Hg). Aspiration of gastric contents into the respiratory tract did not occur, but 19 patients experienced pulmonary complications after operation. The occurrence of vomiting was not noted specifically, but vomiting was rare.

One maternal death occurred 3 weeks after operation, from surgical complications resulting from several operations.

Of 605 patients undergoing Caesarean section not complicated by placenta praevia or premature separation of the placenta, 49 (8%) received blood transfusions (0.15 unit per patient). Of these only three were given 3–4 units because of atony of the uterus after operation. Of 78 patients with placenta praevia or premature separation of the placenta, 41 received blood transfusions, 1.55 unit per patient.

DISCUSSION

The pronounced difference in the frequency of neonatal depression between the groups with optimal and non-optimal conditions before Caesarean section confirmed that it was necessary to estimate the usefulness of an anaesthetic agent in selected patients (Crawford, 1972). Neonatal depression of short duration was rare in the two optimal groups. All the infants in these groups survived.

A significantly greater frequency of RDS occurred in the optimal, elective group when compared with the optimal, emergency group. RDS was also seen more frequently in the non-optimal, elective group than in the non-optimal, emergency group in spite of a higher occurrence of depressed infants in the latter group. These results confirm that elective, but not emergency, Caesarean section increases the frequency of RDS (Robert et al., 1975; Hack et al., 1976), although in this investigation it was unrelated to the anaesthetic agent used. Why elective Caesarean section should increase the frequency of RDS is unknown. There may be a causal relationship with the increased cortisol concentration during established labour (Sybulski and Maugham, 1976a, b; Weekes, Wade and West, 1976). Another possibility is an increased concentration of circulating catecholamines during delivery (Enhorning et al., 1977).

As Caesarean section is often indicated by intrauterine asphyxia or varying degrees of prematurity, or both—indications which necessitate the use of a high percentage of oxygen—it seemed appropriate to use a technique which allowed oxygen approximately 90% to be administered. This is in contrast to almost all other techniques which involve the use of nitrous oxide. Furthermore, cyclopropane is excreted rapidly as compared with residual concentrations of thiopentone, halothane (Johnstone and Breen, 1966; Moir, 1970; Latto and Waldron, 1977), methoxyflurane (Crawford et al., 1976), trichloroethylene (Crawford and Davies, 1975), ketamine (Cane and Sinclair, 1976; Downing et al., 1976), Althesin (Holdcroft et al., 1975), propanidid (Mahomedy et al., 1976) and enflurane (Coleman and Downing, 1975). It is most likely that residual concentration of these agents is without consequences in the mature, normal infant, but may be the limiting factor in respect of survival of the asphyxiated or premature infant (Hodgkinson et al., 1977).

That these may be significant considerations was confirmed by the overall mortality of 7.6% among the premature infants (RDS was the only cause of death in this group). This equalled the mortality seen among premature infants of corresponding birth weight after vaginal deliveries, and was less than that reported by other investigators (Bjerre and Østberg, 1974; Hibbard, 1976; Johnell, Østberg and Wåhlstrand, 1976).

The frequency of awareness in this study was within the same range as in that of Crawford and colleagues (1976) and was independent of the I–D interval. Specific reasons for awareness were present in several of these patients. The two instances of awareness after the most commonly used sequence of thiopentone–nitrous oxide–suxamethonium without supplementation corresponded to the high frequency of awareness reported by others using this technique (Crawford, 1971).

The course of anaesthesia was uncomplicated and lung complications after operation occurred at a frequency similar to that obtained after other types of low abdominal operation.

The lack of relationship between the I–D interval and neonatal behaviour would imply that the surgical intervention can be undertaken without haste as in an ordinary operation—a finding in contrast to the opinion of others (Fothergill, Robertson and Bond, 1971).

The most important objection to the more widespread administration of cyclopropane for Caesarean section is the diminishing use of this drug. One factor which contributes to this development is the risk of explosion, which in Denmark has occurred on three instances among an estimated number of 500 000 anaesthetics with this drug. All were a result of inadequate antistatic precautions. When optimal antistatic conditions are provided and an effective scavenging system is used, the risk of using cyclopropane is minimized.

We concluded from this investigation that cyclopropane, when administered as described, is a useful agent for Caesarean section. It does not depress the neonate or influence the frequency of RDS. It does not hamper the work of the surgeons and is accompanied only occasionally by awareness, which, furthermore, seems to be avoidable if the concentration is increased to 10%.

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CYCLOPROPANE ET OPERATION CESARIENNE

RESUME

Dans une étude de longue durée, 589 patientes ont été anesthésiées par l'inhalation de cyclopropane à 40% pendant 2–3 min. La relaxation a été assurée par le suxaméthonium et l'anesthésie a été entretenue à l'aide de cyclopropane à 7,5%. La série a été partagée en quatre groupes: les patientes dans les meilleures conditions possibles comprenaient 96 cas de chirurgie à froid (groupe 1), 164 cas d'urgence (groupe 3) et celles qui n'étaient pas dans un état optimal comprenaient: 75 cas d'opérations à froid (groupe 2) et 254 cas d'urgence (groupe 4). Tous les bébés inclus dans les groupes 1 et 3 avaient des indices d'Apgar élevés et ont tous survécu. Les bébés inclus dans les groupes 2 et 4 avaient des indices d'Agpar faibles: 8 et 96 respectivement étaient déprimés, alors que 10 et 20 respectivement sont morts par suite de facteurs d'obstétrique et de facteurs relatifs aux nouveaux-nés sans aucune relation avec l'anesthésie. Des syndromes de détresse respiratoire (RDS) se sont développés chez 44 bébés. Parmi les 29 bébés dont le poids à la naissance était inférieur à 2,5 kg, la mortalité a été de 31%, alors qu'aucun décès ne s'est produit sur les enfants venus à terme. La RDS a été plus fréquente après la chirurgie à froid qu'après la chirurgie d'urgence. La dépression des nouveaux-nés a été indépendante de la longueur de l'intervalle de l'induction à l'accouchement dont la moyenne a été de 13,3 min. La fréquence de conscience a été de 1,5%.

ZYKLOPROPAN UND KAISERSCHNITT

ZUSAMMENFASSUNG

In einer Studie wurden 589 Patienten durch die Einatmung von 40% Zyklopropan fur 2–3 Min narkotisiert. Entspannung wurde durch Suxamethonium erzielt, und die Narkose wurde mit 7,5% Zyklopropan aufrechterhalten. Die Patienten waren in vier Gruppen aufgeteilt: Patienten in optimalem Zustand (Gruppe 1, 96 ausgewählte) (Gruppe 3, 164 Notfälle), und solche nicht in optimalem Zustand (Gruppe 2, 75 ausgewählte) (Gruppe 4, 254 Notfälle). Alle Neugeborenen aus Gruppe 1 und 3 zeigten hohe Apgar-Werte und uberlebten durchwegs. Kinder in Gruppe 2 und 4 zeigten niedrigere Apgar-Werte, jeweils 8 und 96 waren unterdrückt, und jeweils 10, bezw. 20 starben aufgrund gynäkologischer und neonataler Faktoren, die nichts mit der Narkose zu tun hatten. Respiratorische Syndrome (RDS) entwickelten sich bei 44 Babies. Bei 29 Babies mit einem Geburtsgewicht von unter 2,5 kg betrug die Sterblichkeit 31%, wogegen es bei ausgereiften Babies zu keinen Todesfällen kam. RDS war wesentlich häufiger bei selbstgewähleten als bei Notfall-Kaiserschnitten. Die neonatale Unterdrückung war unabhängig vom Intervall zwischen Einleitung und Geburt, das durchschnittlich 13,3 Min betrug. Die Bewusstseinshäufigkeit betrug 1,5%.

CICLOPROPANO Y SECCION CESAREA

SUMARIO

En un estudio de investigación, 589 pacientes fueron anestesiados mediante la inhalación de ciclopropano 40% durante 2–3 min. La relajación se logró con suxametonio y la anestesia fue mantenida con ciclopropano 7,5%. La serie fue repartida en cuatros grupos: los pacientes en condiciones óptimas (96 electivos (grupo 1), 164 de emergencia (grupo 3)) y aquellos que no estaban en condiciones óptimas (75 electivos (grupo 2), 254 de emergencia (grupo 4)). Todos los infantes en los grupos 1 y 3 acusaron elevadas marcas Apgar y todos sobrevivieron. Los infantes en los grupos 2 y 4 presentaron marcas Apgar inferiores, 8 y 96 respectivamente estuvieron deprimidos; 10 y 20 fallecieron a consecuencia de factores obstétricos y neonatales no relacionados con la anestesia. En 44 infantes se presentó el síndrome de angustia respiratoria (RDS). Entre 29 infantes cuyo peso de nacimiento fue inferior a 2,5 kg, la mortalidad fue de un 31%, mientras que no se produjeron muertes entre los infantes maduros. La frecuencia del RDS fue significativamente mayor siguiendo cirugía electiva que después de la cirugía de emergencia. La depresión neonatal no se relacionó con el período de inducción-parto, que promedió 13,3 min. La frecuencia de conocimiento fue de 1,5%.

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HYPOTENSIVE ANAESTHESIA FOR CRANIECTOMY IN INFANCY

J. H. DIAZ AND C. H. LOCKHART

SUMMARY

Deliberate hypotension using halothane and controlled ventilation without positive end-expiratory pressure was employed in 18 of 30 patients undergoing craniectomy for unilateral or bilateral craniosynostosis over a 3-yr period. The technique was simple, resulted in good control of arterial pressure and diminished blood loss, and did not involve extensive monitoring or the use of potentially toxic adjuvant drugs. In the hypotensive group mean systolic arterial pressure was decreased from 92.5 to 65.0 mm Hg. Estimated blood loss was decreased from 111 to 89 ml (mean) for all ages and from 133 to 72 ml (mean) for infants between 8 and 32 weeks of age compared with the normotensive control group.

Premature closure of cranial sutures may occur *in utero*, resulting in a cosmetically deformed baby. Synostosis of two or more sutures may cause severe craniofacial deformity and visual and central nervous system disturbance as a result of intracranial hypertension during periods of rapid brain growth (Hanson et al., 1977). Early surgical decompression by strip craniectomy is recommended to allow for normal brain growth in cases of multiple craniosynostoses and to prevent serious cosmetic deformity in cases of single or two-suture synostosis (Freeman and Borkowf, 1962; Shillito and Matson, 1968).

Craniectomy in infancy, although usually a cosmetic operation, is not without risk. Shillito and Matson (1968) have reported mortality of 0.39% and morbidity of 14.0% in a large series of 519 patients undergoing a total of 689 operations over 33 yr.

Anaesthesia for craniectomy can be hazardous. The anaesthetist must monitor a significant blood loss (the two deaths in Shillito's series resulted from hypovolaemic cardiac arrest) and maintain an adequate airway despite lack of access to the face.

PATIENTS AND METHODS

Thirty patients undergoing craniectomy between March 1975 and April 1978 are reported. Eighteen received a deliberate hypotensive technique in an attempt to reduce total blood loss and to improve operating conditions. Twelve remained normotensive with the same anaesthetic agents. All the surgery was elective, upon infants with single or double craniosynostoses and no clinical or x-ray evidence of increased intracranial pressure.

The mean age of the normotensive group was 14.58 weeks (SD ± 8.53); mean weight 6.5 kg (SD ± 1.29). The mean age of the hypotensive group was 10.83 weeks (± 4.12); mean weight of 5.94 kg (± 0.53). The youngest patient was 3 weeks old (hypotensive group) and the oldest 32 weeks (normotensive group). The patients fasted for 4 h before operation and no premedication was given.

Patients were selected for the groups randomly. Both normotensive and hypotensive groups consisted mainly of operations involving the sagittal suture. Two operations not completely involving the sagittal suture were included in each group.

Anaesthesia was induced with halothane and an Oxford-pattern oral tracheal tube was inserted following the administration of a neuromuscular blocking drug. Ventilation was assisted initially then controlled manually using a Mapleson D circuit and a 500-ml capacity reservoir bag. Positive end-expiratory pressure (PEEP) was not employed and zero end expiratory pressure was confirmed in several cases by continuous manometric monitoring at the tracheal tube. Normothermia (continuous rectal temperature) was maintained by environmental temperature control, heating blankets and overhead heating lamps when indicated.

Systolic arterial pressure was monitored with a Doppler ultrasonic device. Lead II of the e.c.g. was displayed continuously. Blood loss was measured by weighing all sponges and using calibrated suction traps. In all instances, blood was replaced meticulously when losses exceeded 10–15% of estimated

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total blood volume (80.0 ml per kg body weight). The neurosurgeons occasionally infiltrated the skin incision sites with sterile saline which did not contain a vasoconstrictor.

Twenty-nine patients were managed in the supine position with a slight (25°) head-up tilt. One patient was moved from the supine to the prone position for correction of unilateral lambdoidal synostosis.

Anaesthesia was maintained in all infants with halothane and 40–60% nitrous oxide in oxygen.

Hypotension was induced gradually and maintained with halothane alone; no adjuvant drugs were used. Lactated Ringer's solution in 5% dextrose was administered at a rate of 5–7 ml per kg of body weight per hour. Data were analysed statistically using Student's paired t test.

RESULTS

Systolic arterial pressure. The mean systolic arterial pressure before operation in the normotensive group was 83.5 mm Hg (SD ± 16.0). The mean intraoperative systolic arterial pressure in this group was 83.8 mm Hg (± 20.3). In the hypotensive group, halothane concentration was increased gradually (Ohio copper kettle vaporizers, temperature 25.0 °C) resulting in a significant decrease in mean systolic arterial pressure from 92.5 to 65.0 mm Hg ($P < 0.05$). No arrhythmia and no significant increases in heart rate were encountered during hypotension.

Halothane concentration. The mean dose of halothane required to maintain normotensive surgical anaesthesia was 1.13% (± 0.27). The mean dose of halothane required to produce a significant reduction in systolic arterial pressure was 1.40% (± 0.42) in patients less than 8 weeks of age ($n = 6$) and 1.33% (± 0.89) in patients 8 weeks of age or older (n = 12).

Total intraoperative blood loss. Mean intraoperative blood loss in the normotensive group was 111 ml (± 97) and in the hypotensive group 89 ml (± 53) ($P < 0.05$). This difference was more marked in patients 8 weeks of age and older: 133 ml (± 103) with normotensive anaesthesia and 72 ml (± 39) with hypotension ($P < 0.001$). Three of the 18 hypotensive patients did not require transfusion as blood loss was less than 10% of the estimated preoperative blood volume. Of these three infants, the operation in only one did not involve the sagittal suture, and was confined to a single coronal closure.

Haematological changes. The haemoglobin concentration and hematocrit before operation in the normotensive group were 12.7 g% (± 0.9) and 36.2% (± 2.6) respectively. The respective values 24 h after operation were 11.2 g% (± 1.4) and 32.3% (± 4.1). In the hypotensive group the values before operation were 12.7 g% (± 1.4) and 36.7% (± 4.8) and the values 24 h after operation were 11.0 g% (± 1.9) and 32.1% (± 5.6).

Because of the higher concentrations of fetal haemoglobin in those patients less than 8 weeks of age, the effect of age was assessed. Infants less than 8 weeks of age had insignificantly greater haemoglobin and haematocrit values that did not alter anaesthetic management, blood loss or surgical outcome.

Complications. There were no deaths. One patient in the normotensive group suffered excessive blood loss (81.8% of preoperative estimated blood volume) and this was replaced as it occurred, without incident. Subsequent complete coagulation studies were normal. One patient in the hypotensive group had a wound dehiscence on the 5th day after operation and this required re-operation for débridement.

Other observations. Sex, familial incidence and sutures involved were studied also. In no instance was there a family history of craniosynostosis. There were, however, no cases of Crouzon's or Apert's disease, both inheritable craniofacial diseases that also exhibit craniosynostosis. The male : female ratio was 1.7 : 1.0. Single sagittal synostosis was present in 84.2% of the males and 81.8% of the females. There were 25 infants with single sagittal craniosynostosis, the most common deformity in all reported series. There were two infants with bilateral coronal synostosis, one with unilateral coronal synostosis, one with unilateral coronal and sagittal synostosis, and one with unilateral coronal and unilateral lambdoidal synostosis.

The total estimated blood loss for craniectomy not completely involving the sagittal suture was not significantly less than that for parasagittal craniectomy in the same group.

DISCUSSION

In their large series, Shillito and Matson (1968) noted sagittal synostosis to be five times more common than any other type of craniosynostosis. The frequencies of single coronal and bilateral coronal closures were next and nearly equal. Other combinations were rare.

In paediatric centres, craniectomy for craniosynostosis is no longer an uncommon neurosurgical procedure in infancy. At The Children's Hospital of Denver, craniectomy is the third most common neurosurgical procedure in infancy following ventriculo-peritoneal shunting and repair of meningomyelocoele.

The procedure is usually elective in an otherwise healthy infant and carries a significant risk of massive haemorrhage from dural venous sinuses and exposed bone, especially during parasagittal craniectomy (the most common procedure). Deliberate hypotension using halothane with controlled ventilation appears safe without requiring excessive doses of drug and is effective in reducing blood loss. This technique does not appear to be associated with the cardiovascular complications often encountered with the use of multiple hypotensive adjuvant drugs (McNeil et al., 1974; Salem et al., 1974).

Although it may augment induced hypotension by reduction in preload, the use of PEEP appears to be contraindicated in these patients as it may increase significantly cerebral venous pressures and promote unnecessary venous haemorrhage.

The intraoperative monitoring described for this technique is simple yet accurate and does not necessitate arterial invasion. The use of skin infiltration with adrenaline can be avoided, and blood loss observations and replacement can be accomplished accurately. Transfusion may even be avoided in some patients, especially those undergoing procedures not involving the sagittal suture.

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ANESTHESIE HYPOTENSIVE POUR LA CRANIECTOMIE CHEZ LES BEBES

RESUME

On a utilisé, au cours d'une période de 3 ans, sur 18 patients (sur un total de 30) subissant une craniectomie pour une craniosynostose unilatérale ou bilatérale, une technique d'hypotension délibérée à l'aide d'halothane et de ventilation contrôlée sans pression expiratoire à l'extrémité positive. Cette technique, qui est simple, a permis d'avoir un bon contrôle de la tension artérielle et de réduire les pertes de sang. Elle n'a exigé ni surveillance excessive ni l'usage de médicaments adjuvants potentiellement toxiques. Dans le groupe hypotensif, la tension artérielle systolique moyenne est tombée de 92,5 à 65 mm Hg. La perte de sang estimée a été réduite de 111 à 89 ml (en moyenne) pour tous les âges et de 133 à 72 ml (en moyenne) pour les bébés âgés de 8 à 32 semaines, ceci par comparaison au groupe témoin normotensif.

HYPOTENSIVE ANÄSTHESIE FÜR KRANIEKTOMIE BEI KINDERN

ZUSAMMENFASSUNG

Beabsichtigte Hypotension unter Verwendung von Halothan und kontrollierter Belüftung ohne positiven Endausatmungsdruck wurde benutzt, um und zwar bei 18 von 30 Patienten, bei denen über einen Zeitraum von 3 Jahren wegen unilateraler oder bilateraler Kraniosynostosis eine Kraniektomie vorgenommen wurde. Die verwendete Technik war einfach, führte zu guter Kontrollierbarkeit des arteriellen Druckes und zu verringertem Blutverlust, und erforderte keine umfassende Überwachung und keine Verwendung potentiell toxischer Hilfsdrogen. Bei der hypotensiven Gruppe verringerte sich der mittlere systolische arterielle Druck von 92,5 auf 65,0 mm Hg. Der geschätzte Blutverlust wurde von 111 auf 89 ml verringert, das ist der Mittelwert für alle Altarsgruppen, und von 133 auf 72 ml, das ist der Mittelwert für Kinder zwischen 8 und 32 Wochen, verglichen mit der normotensiven Kontrollgruppe.

ANESTESIA HIPOTENSIVA PARA CRANIECTOMIA EN LA INFANCIA

SUMARIO

Se empleó hipotensión deliberada mediante la aplicación de halotano y ventilación controlada sin presión positiva y expiratoria, en 18 de 30 pacientes sometidos a craniectomía para craniosinostosis unilateral o bilateral durante un período de 3 años. La técnica fue sencilla y produjo buen control de la presión arterial, redujo la pérdida de sangre y no comprendió un extenso control del empleo de drogas coadyuvantes potencialmente tóxicas. En el grupo hipotensivo, la presión arterial sistólica media fue disminuida de 92,5 a 65,0 mm Hg. La pérdida de sangre calculada fue disminuida de 111 a 89 ml (medio) para todas las edades y de 133 a 72 ml (promedio) para los infantes de 8 a 32 semanas de edad, en comparacíon con el grupo normotensivo de control.

Br. J. Anaesth. (1979), **51**, 237

METALLIZED PLASTIC SHEETING IN THE PREVENTION OF HYPOTHERMIA DURING NEUROSURGERY

P. RADFORD AND A. C. THURLOW

SUMMARY

Metallized plastic sheeting (m.p.s.) was found to be ineffective in the prevention of hypothermia in adult patients studied during neurosurgical operations. Twenty patients were wrapped in m.p.s. and 22 patients acted as controls. Mean oesophageal temperature in the m.p.s. group decreased from 36.2 °C to 35.4 °C after 3 h (control 36.5 °C to 35.4 °C). It was concluded that active warming systems are needed to maintain normothermia in patients undergoing neurosurgical operations.

Surgeons are most comfortable when the operating theatre temperature is 18 °C whereas anaesthetists prefer a temperature of 22 °C (Wyon, Lidwell and Williams, 1968). Morris and Wilkey (1970) showed that anaesthetized patients became hypothermic if the environmental temperature was less than 21 °C and Morris (1971) found that a significant proportion became hypothermic if the temperature in the operating theatre was between 21 and 24 °C. Thus, most anaesthetized patients will become hypothermic unless the temperature of the room is greater than that producing optimal working conditions.

The following techniques have been described in the attempt to decrease the loss of heat in patients during surgery:

- pre-warmed gel-filled mattresses (Winder and Vale, 1970),
- blankets with circulating warm liquid (Newman, 1971; Morris and Kumar, 1972),
- suits with circulating warm liquid (Goldblatt and Miller, 1972),
- humidification of inspired gases (Newton, 1975), and
- metallized plastic sheeting (m.p.s.) (Dyde and Lunn, 1970).

Since active methods of warming carry the risks of overheating or burning patients and humidification increases the risk of bacterial contamination in the breathing circuit, we decided to look further at the value of m.p.s.

The type of m.p.s. studied was the heavier of the two made by Thermos under the name of "Space Blanket". Each blanket consists of two layers of m.p.s. separated by an artificial fibre layer and measures 2.11 m by 1.42 m. Dyde and Lunn (1970) had used m.p.s. previously in thoracic surgery but, although several neurosurgical centres in this country use m.p.s. routinely, there is no report of its use in neurosurgery.

METHODS

All the patients studied were undergoing craniotomy for intracranial tumours or aneurysms at Atkinson Morley's Hospital, London. Patients less than 14 years old and those with pyrexia before operation were excluded. Surgery was performed with all patients in the supine position. The patients were allocated randomly to a study group (m.p.s.) or a control group (without m.p.s.).

The patients were premedicated with either atropine 0.3–0.6 mg or hyoscine 0.2–0.4 mg given i.m. Patients with intracranial aneurysms and a normal level of consciousness were given papaveretum 10 mg i.m. at the same time.

Anaesthesia was induced, in the anaesthetic room, with thiopentone or methohexitone. Suxamethonium 100 mg was given to facilitate the passage of an armoured latex orotracheal tube. Anaesthesia was maintained with nitrous oxide in oxygen, supplemented by halothane (up to 0.5%) in some patients, and a narcotic, in all patients. Artificial ventilation of the lungs was performed using a Cape–Waine ventilator. Tubocurarine was given to produce neuromuscular blockade which was antagonized at the end of the operation by the administration of atropine and neostigmine. If necessary an infusion of trimetaphan was used to provide arterial hypotension.

Venous and arterial cannulae were inserted in the

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anaesthetic room. Throughout the operation arterial pressure and the e.c.g. were monitored.

Following intubation, a thermocouple temperature probe was passed into the oesophagus. It was positioned so that its tip was estimated to be at the nipple line. This was taken to approximate to the mid-oesophageal point. The first temperature recording occurred as soon as the patient had been moved into the operating theatre and placed on the operating table.

Each patient wore a cotton gown and was covered by one cotton blanket. In addition, each patient in the study group was wrapped in m.p.s. The head and shoulders were left exposed, as was the distal part of any limb with an arterial or venous cannula in place. Oesophageal temperature was noted (to the nearest 0.1 °C) hourly until completion of surgery. Theatre temperature was noted (to the nearest 1 °C) at the beginning and the end of the operation. No active warming system was used. The anaesthetic gases were not warmed or humidified. Infused blood, which was given rarely, was warmed; other infusions were not warmed.

Two Sierex and one Roche oesophageal temperature probes were used in the study. Each had been checked against a mercury-in-glass thermometer, through the appropriate range. Room temperature was measured using an alcohol-in-glass thermometer hung in the same position in each of the two theatres used.

RESULTS

Forty-two patients were studied of whom 20 were in the study group (with m.p.s.) and 22 were in the control group (without m.p.s.).

Table I lists relevant general data. The two groups were similar in sex distribution, age, intracranial pathology, time from induction to first temperature measurement, theatre temperature, use of halothane, use of trimetaphan and initial temperature.

TABLE I. *Distribution of potentially relevant factors*

	Study group	Controls
Total number of patients	20	22
Sex: % male	55	50
Age (yr) (mean ± SD)	48 ± 15	49 ± 13
% with intracranial aneurysm	35	50
Time from induction to first temp. (min) (mean ± SD)	26 ± 6	25 ± 12
Theatre temp. (°C) (mean ± SD)		
beginning operation	22.1 ± 1.5	22.3 ± 1.9
end operation	23.3 ± 1.6	24.1 ± 2.0
Halothane (%) use	80	91
Trimetaphan (%) use	55	73
First oesophageal temp. (°C) (mean ± SD)	36.20 ± 0.54	36.49 ± 0.66

Table II shows the decreases observed in the oesophageal temperature at 1, 2 and 3 h relative to the initial measurements. There was only 0.01 °C difference between the changes in mean temperature in the two groups at 1 h. At 2 h there was no difference. At 3 h the decrease was greater in the control group (1.18 °C) than in the study group (0.94 °C), however, this difference was not significant (Student's *t* test, $P > 0.05$).

TABLE II. *Oesophageal temperature during operation*

	Study group	Controls
No. of patients		
initially	20	22
at 1 h	20	22
at 2 h	18	21
at 3 h	7	13
Oesophageal temp. (°C) (mean ± SD)		
initially	36.20 ± 0.54	36.49 ± 0.66
at 1 h	35.67 ± 0.57	35.95 ± 0.59
at 2 h	35.56 ± 0.43	35.70 ± 0.78
at 3 h	35.44 ± 0.62	35.35 ± 0.89
Overall temp. decrease (°C) (mean ± SD)		
at 1 h	0.53 ± 0.28	0.54 ± 0.36
at 2 h	0.79 ± 0.45	0.79 ± 0.56
at 3 h	0.94 ± 0.60	1.18 ± 0.54

DISCUSSION

Our results show that m.p.s. was not effective in preventing core hypothermia during neurosurgery.

Temperature changes during operation are affected by age, the nature of operation, the type of anaesthetic and the ambient temperature (Goldberg and Roe, 1966; Goldblatt and Miller, 1972). Holdcroft and Hall (1978) found, however, that the decrease in temperature was not always related to the type of anaesthetic used or to body fat cover. The two groups in this trial were similar in respect of relevant factors. Thus, it is unlikely that the results have been biased by a difference between the groups in an important variable.

Our clinical impression before this trial was that m.p.s. was effective in reducing heat loss during neurosurgery. Indeed, Dyde and Lunn (1970) found that the use of m.p.s. reduced the decrease in deep and surface temperatures in patients during thoracic operations. However, they measured deep temperature in the nasopharynx and rectum, sites that are less reliable than the oesophagus (Hall, 1978). Their control and study groups, which were small and not similar in sex ratios or duration of operation, were consecutive and not concurrent. Unlike Dyde and Lunn, we did not measure surface temperature and so cannot say whether m.p.s. has any effect on its maintenance.

Whitby and Duncan (1971) did show that the lowest fourth of the oesophagus was the optimal site for temperature measurement and corresponds most closely with the temperature of the brain. While it is accepted that the mid-oesophageal site can be affected by cooling as a result of ventilation, in this trial the tidal volumes and rates of ventilation were similar in both groups. Thus, we feel that it is unlikely that any cooling by ventilation would invalidate the comparison.

M.p.s. works by reducing the heat loss caused by radiation. However, the main loss of heat from the body is by convection. Another theoretical drawback of m.p.s. is that the infra-red reflecting property of the metallic surface is reduced by condensed perspiration. Therefore, it is not surprising that m.p.s. is of little value in preventing hypothermia during neurosurgery. Indeed, Marcus (1977) found that m.p.s. was not effective as an aid to survival in a cold climate.

Inadvertent hypothermia is a serious problem in neurosurgery because of the duration of the operation. Although induced hypothermia has been used to protect the brain from transient ischaemia the technique is now used less frequently because of the lack of demonstrable benefit. It is unlikely that the mild hypothermia shown to occur in patients in this trial would have any protective effect. Indeed, it is our impression that patients undergoing neurosurgery and who are cold are more likely to develop acute arterial hypertension, which has potentially dangerous consequences, immediately after surgery than are those who are warm.

Hall (1978), in a review article, emphasized the dangers of allowing an anaesthetized patient to cool. Benzinger (1967) established that, if the core temperature becomes less than 37 °C and the superficial temperature is less than 33 °C, there is an increase in metabolic rate. It seems reasonable to believe that this increase may cause the cardiovascular or respiratory reserves of an ill patient to be exceeded. Roe and others (1966) demonstrated that oxygen consumption in the period soon after operation was greater if the patients were cold.

Another potential danger with hypothermia during anaesthesia is that there may be difficulties with neuromuscular blocking drugs and their antagonism (Miller, Van Nyhuis and Eger, 1975; Miller and Roderick, 1977).

Therefore, on balance, it seems desirable to keep the body temperature of neurosurgical patients normal. We have shown that a passive system, such as the use of m.p.s., is unable to do this if the theatre temperature is comfortable for the staff. A system for active warming of the patient is needed. It is probable that the low initial temperature of our patients resulted from cooling during induction and insertion of arterial and venous lines. Ideally, therefore, a warming system should be put into use before the induction of anaesthesia.

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FEUILLE DE PLASTIQUE METALLISE POUR LA PREVENTION DE L'HYPOTHERMIE PENDANT LA NEUROCHIRURGIE

RESUME

On a trouvé qu'une feuille de plastique métallisé (m.p.s.) était inefficace pour prévenir l'hypothermie chez les malades adultes que l'on a surveillés pendant des opérations neurochirurgicales. On a enveloppé 20 malades dans du m.p.s. alors que 22 autres malades ont servi de témoins. La température oesophagienne moyenne a diminué dans le groupe m.p.s. de 36,2 °C à 35,4 °C après 3 h (alors que les témoins indiquaient 36,5 °C/35,4 °C). Il en a été conclu qu'il faut des systèmes de chauffage actif pour maintenir la normothermie chez les patients subissant des interventions neuro-chirurgicales.

METALLISIERTE KUNSTSTOFFTÜCHER ZUR VERHUTUNG VON HYPOTHERMIE BEI NEUROCHIRURGIE

ZUSAMMENFASSUNG

Metallisierte Kunststofftücher (m.p.s.) erwiesen sich als unwirksam fur die Verhütung von Hypothermie bei erwachsenen Patienten, die während Neurochirurgie studiert wurden. Zwanzig Patienten wurden in m.p.s. gewickelt, während 22 andere Patienten als Kontrollgruppe fungierten. Die mittlere Speiseröhrentemperatur in der m.p.s.-Gruppe sank nach 3 Stunden von 36,2 auf 35,4 °C (Kontrollgruppe von 36,5 auf 35,4 °C). Man schliesst, dass aktive Wärmsysteme erforderlich sind, um bei neurochirurgischen Eingriffen eine Normothermie bei den Patienten zu bewahren.

HOJAS PLASTICAS METALIZADAS PARA LA PREVENCION DE HIPOTERMIA DURANTE NEUROCIRUGIA

SUMARIO

Se descubrió que las hojas plásticas metalizadas (m.p.s.) son inefectivas en la prevención de hipotermia en los pacientes adultos estudiados durante operaciones neuroquirúrgicas. Veinte pacientes fueron envueltos en m.p.s. y 22 pacientes sirvieron de controles. La temperatura esofagal media en el grupo de m.p.s. disminuyó desde 36,2 a 35,4 °C al cabo de 3 h (control desde 36,5 a 35,4 °C). Se concluyó que se requieren sistemas activos de calentamiento para conservar normotermia en pacientes sometidos a operaciones quirúrgicas.

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SUXAMETHONIUM INFUSION RATE AND OBSERVED FASCICULATIONS

A dose–response study

A. FEINGOLD AND J. L. VELAZQUEZ

SUMMARY

Suxamethonium chloride (Sch) was administered i.v. to 36 adult males at six rates: 0.25 mg s^{-1} to 20 mg s^{-1}. The infusion was discontinued either when there was no muscular response to tetanic stimulation of the ulnar nerve or when Sch 120 mg was exceeded. Six additional patients received a 30-mg i.v. bolus dose. Fasciculations in six areas of the body were scored from 0 to 3 and summated as a total fasciculation score. The times to first fasciculation, twitch suppression and tetanus suppression were inversely related to the infusion rates. Fasciculations in the six areas and the total fasciculation score were related directly to the rate of infusion. Total fasciculation scores in the 30-mg bolus group and the 5-mg s^{-1} and 20-mg s^{-1} infusion groups were not significantly different.

Muscle fasciculations are commonly observed as the earliest clinical sign of the onset of neuromuscular blockade following a bolus i.v. dose of suxamethonium (Sch). Fasciculations are observed less consistently following the administration of Sch by slow i.v. infusion, i.m. injection or after pretreatment with a non-depolarizing muscle relaxant drug. This investigation was designed to study systematically the temporal and quantitative relationships between the rate of i.v. infusion of Sch muscle, fasciculations and the onset of neuromuscular blockade.

METHODS

Thirty-six adult male patients undergoing elective surgery for which endotracheal intubation was a requisite were assigned randomly to one of six Sch infusion groups: 0.25 mg s^{-1}, 0.50 mg s^{-1}, 1 mg s^{-1}, 2 mg s^{-1}, 5 mg s^{-1}, 20 mg s^{-1}. An additional six patients received a 30-mg bolus dose of Sch.

Induction of anaesthesia was with a dose of thiopentone sufficient to abolish the eyelid reflex. Ventilation of the lungs was assisted and then controlled, the inspired gas being 60% nitrous oxide in oxygen. Needle electrodes were placed over the ulnar nerve at the wrist and supramaximal stimulation was obtained with a Block-Aid Monitor (Burroughs Wellcome Co.). The Sch infusions were administered from a calibrated syringe pump (Model 990, Harvard Equipment Co.) connected to 16- or 18-gauge i.v. cannulae, 2 cm from the venepuncture site on the forearm, wrist or hand. Sch solutions were prepared from crystals (Anectine, Burroughs Wellcome Co.) dissolved in 5% dextrose solution in water and were refrigerated between use. Three observers watched for fasciculations at the six designated areas: eyes, face and neck, arms and hands, legs, toes and abdomen. One of these observers operated the nerve stimulator and watched the response to twitch and tetanic stimulation. Infusions were continued beyond the point of no observed response to twitch stimulation (twitch suppression) until there was either no observed response to tetanic stimulation (tetanus suppression) or Sch 120 mg was exceeded.

The measured variables included age, weight, height, physical status (ASA classification), dose of thiopentone, total dose of Sch, time to first fasciculation, time to twitch suppression and time to tetanus suppression. Fasciculations were scored as: 0 = absent, 1 = slight, 2 = moderate and 3 = gross movement. The total fasciculation score was the sum of the six fasciculation scores. Statistical analyses were carried out using either the Spearman rank correlation coefficient or the Median test for the ordinal data (fasciculation scores) and the *F* test analysis of variance for the remaining data.

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RESULTS

The time to first fasciculation, twitch suppression and tetanus suppression were related inversely to the rates of infusion of Sch ($P < 0.05$; table I). The total fasciculation scores were related directly to the rates of infusion of Sch ($P < 0.05$; table II). Observable fasciculations occurred over one or more areas in all but five patients. These five patients were in the two slowest infusion groups (table I).

For the 0.25-, 0.50- and 1-mg s^{-1} infusion groups, the doses of Sch for tetanus suppression were related directly to the infusion rates ($P < 0.05$). For the 2.0-, 5.0- and 20-mg s^{-1} infusion groups, the maximum dose of Sch was exceeded before fasciculations were observed.

The total fasciculation scores from the 30-mg Sch bolus were not significantly different from those obtained in the 5-mg s^{-1} and 20-mg s^{-1} infusion groups. The observations of twitch and tetanus suppression following the 30-mg bolus of Sch were variable and were not included in the final data. There were no significant correlations ($P > 0.05$) between the remaining measured variables and either the Sch infusion rates or the total fasciculation scores. The mean (± SEM) values were: weight, 73 (±2.0) kg; height, 175 (±3.0) cm; thiopentone dose, 294 (±16.0) mg; and ASA physical status classification, 2.3 (±0.1). The ages are shown in table I.

TABLE I. *Relationships between measured variables (mean ± SEM) and the rates of infusion of Sch*

	Sch infusion rates (mg s^{-1})						30-mg bolus
Measured variables	0.25	0.50	1.0	2.0	5.0	20.0	
Age (yr)	54 ±3	53 ±4	58 ±3	55 ±5	53 ±7	54 ±7	50 ±6
Time to first fasciculation (s)*	91 ±24	59 ±13	58 ±6	54 ±9	41 ±5	36 ±5	31 ±7
Time to twitch suppression (s)	169 ±21	121 ±13	106 ±7	84 ±6	92 ±7	73 ±6	—
Time to tetanus suppression (s)*	194 ±21	140 ±13	126 ±15	150 ±11	97 ±7	87 ±7	—
Dose of suxamethonium to tetanus suppression (mg)*	47 ±5	76 ±7	113 ±7	120	120	120	—
Number of patients having observable fasciculations	3	4	6	6	6	6	6

* F test analysis of variance for five degrees of freedom; $P < 0.05$.

TABLE II. *Median fasciculation scores with ranges in parentheses*

	Sch infusion rates (mg s^{-1})						30-mg bolus
	0.25	0.50	1.0	2.0	5.0	20.0	
Eyes	0 (0–1)	0 (0–1)	0 (0–1)	0 (0–1)	0.5 (0–1)	1.0 (1–2)	1.0 (0–2)
Face and neck	0 (0–1)	0.5 (0–2)	1.0 (0–2)	0.5 (0–2)	1.5 (0–3)	1.5 (1–2)	1.0 (1–2)
Arms and hands	0 (0–2)	0.5 (0–2)	0 (0–1)	1.0 (1–2)	1.0 (1–3)	3.0 (1–3)	2.0 (1–3)
Abdomen	1 (0–2)	0.5 (0–2)	1.0 (0–2)	0.5 (0–2)	1.5 (1–3)	2.0 (2–3)	2.0 (1–2)
Legs	0 (0–1)	0	0 (0–1)	0 (0–1)	1.0 (0–3)	2.0 (1–3)	1.5 (0–3)
Toes	0 (0–2)	1.0 (0–2)	0 (0–1)	0 (0–2)	1.0 (1–3)	2.0 (1–3)	1.0 (0–2)
Total fasciculation score*	1.0 (0–9)	2.5 (0–8)	2.5 (2–4)	2.5 (1–8)	7.5 (4–16)	11.5 (8–13)	9.5 (3–13)

* Spearman rank correlation coefficient; $P < 0.05$.

DISCUSSION

The relationship between the rate of infusion of Sch and the magnitude of fasciculation was observed during the earliest clinical studies. Foldes, McNall and Borrego-Hinojose (1952) suggested that a slow i.v. infusion, in contrast with a rapid bolus dose, would usually prevent muscle fasciculations. Helmsworth and Schotz (1955) reported that, "the muscle tremors often seen . . . can be avoided by the dilute i.v. drip technique which appears to be rapid enough for any purpose".

Grading the magnitude of fasciculations in four levels from absent to severe was used by Lamoreaux and Urbach (1960) and by Pauca, Reynolds and Strobel (1975). In the latter study, 18 patients received an infusion of Sch 0.58 mg s^{-1}. Their observations of three patients without fasciculations, three with minimal fasciculations, six with moderate fasciculations and six patients with gross movements are consistent with our results.

The use of several observers and the summing of observations over different parts of the body were unique features of our study. The eye region was not capable of gross movement and a score of 3 was not possible. Although the maximum total fasciculation score was 17, the greatest total fasciculation score in an individual patient was 16, in the 5-mg s^{-1} infusion group. Gross movements (score 3) were observed most frequently over the abdomen and arms. Mild to moderate fasciculations (score 1 or 2) were observed most frequently over the face, neck, hands and feet. Fasciculations were occasionally observed only at the hands and feet and these may have been missed had not all areas been observed simultaneously.

Minimal to mild fasciculations were observed in half the patients in our slowest infusion group (0.25 mg s^{-1}). The absence of, or minimal, fasciculations at 0.1 mg s^{-1} observed by Helmsworth and Schotz (1955), McNally, Neily and Benoit (1962) and Ieri, Pallini and Frullani (1966) confirm that much slower infusions are required to abolish observable fasciculations.

The latent time to fasciculation was related inversely to the rate of infusion of Sch. Times of 31 s observed after the 30-mg bolus of Sch and 36 s after the 20-mg s^{-1} infusion rate agree with the 30–45 s reported in the study of Foldes. Yamaguchi (1973) and Yamaguchi, Namiki and Yamachita (1974) demonstrated correlations between the latent times to fasciculations and two measures of circulation time. The former were approximately twice the latter and all three variables were directly related to age. In their 51- to 71-year-old group, the mean latent time to fasciculation was 28.7 s.

This study shows that the onset of neuromuscular blockade, measured either by the latent time to abolition of twitch or tetanus, is related inversely to the rate of infusion of Sch. This probably limits the clinical usefulness of Sch infusion techniques to situations in which rapid paralysis is not necessary. The mean times to twitch and tetanus suppression of 73 and 87 s respectively in our fastest infusion group (20 mg s^{-1}) compares favourably with the mean time to 95% twitch suppression of 81 s after 1-mg kg^{-1} bolus doses of Sch reported by Harrison and Junius (1972). However, Pauca, Reynolds and Strobel (1975), using a 0.58-mg s^{-1} infusion of Sch, measured an average of 59.2 s to 100% twitch suppression. This latent time is significantly shorter than that observed in our study and might result from the younger age of their patients (mean age, 29 yr).

Fasciculations are observed less frequently when Sch is administered i.m. (Cooke et al., 1963). There may be an infusion rate at which the latent time to paralysis and the magnitude of fasciculation might be expected to resemble the administration of Sch i.m. Walts and Dillon (1967) found that the mean latent time to complete twitch suppression following i.m. injections of Sch 4 mg kg^{-1} into the deltoid muscle was 108 s. This latent time to twitch suppression occurred at our infusion rate of Sch 1 mg s^{-1}. Walts and Dillon did not study fasciculations, but all patients in our 1-mg s^{-1} group had observable fasciculations.

The relationship between the magnitude of fasciculations and the severity of myalgia after operation remains controversial. Some investigators have reported a decreased frequency of fasciculations and myalgias after operation when Sch is infused slowly (McNally, Neily and Benoit, 1962; Ieri, Pallini and Frullani, 1966). Others have reported the absence of a relationship (Churchill-Davidson, 1954; Morris and Dunn, 1959; Lamoreaux and Urbach, 1960; Halldin and Palmer, 1961). The relationships between the magnitude of fasciculations and increased intraocular pressure (Schwartz and DeRoetth, 1958; Meyers et al., 1978) increased intragastric pressure (LaCour, 1970), arrhythmia (Winter and Ahnefeld, 1974) and electromyographic recordings (Collier, 1975) also remain controversial.

The slow i.v. infusion of Sch at rates less than 2 mg s^{-1} appears to offer a clinical method for reducing observable fasciculations and perhaps diminishing some of the deleterious sequelae of the administration of Sch. This potential advantage is balanced by the disadvantage of a delayed onset of neuromuscular blockade.

ACKNOWLEDGEMENTS

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TAUX D'INFUSION DU SUXAMETHONIUM ET FASCICULATIONS OBSERVEES

Etude dose–réaction

RESUME

On a administré par voie intraveineuse du chlorure de suxaméthonium (Sch) à 36 hommes adultes, à six différentes doses comprises entre 0,25 mg s^{-1} et à 20 mg s^{-1}. L'infusion a été arrêtée soit lorsqu'il n'y a plus eu de réaction musculaire à la stimulation tétanique du nerf ulnaire, soit lorsque la dose de 120 mg de Sch a été dépassée. Six autres patients en ont reçu par voie intraveineuse une dose de 30 mg. On a attribué des points allant de 0 à 3 aux fasciculations se produisant sur six parties du corps et on en a fait le total. Les temps nécessaires à l'obtention de la première fasciculation, à la suppression de la crispation et à la suppression de la réaction tétanique ont été inversement liés aux taux d'infusion. Les fasciculations dans les six parties du corps et le total des points relevés lors des fasciculations ont été directement liés au taux d'infusion. Le total des points attribués aux fasciculations constatées dans le groupe ayant reçu un bol de 30 mg ainsi que dans les groupes ayant reçu des infusions de 5 mg s^{-1} et de 20 mg s^{-1} n'a pas différé significativement.

SUXAMETHONIUM-INFUSIONSRATE UND BEOBACHTETE FASZIKELBILDUNG

Eine Dosierungs studie

ZUSAMMENFASSUNG

Suxamethoniumchlorid (Sch) wurde intravenös 36 erwachsenen Männern in sechs Raten verabreicht: von 0,25 mg s^{-1} bis 20 mg s^{-1}. Die Infusion wurde beendet, wenn es entweder zu keiner Muskelreaktion auf tetanische Stimulierung des Ulnarnervs kam, oder wenn 120 mg Sch überschritten wurden. Sechs weitere Patienten erhielten eine 30 mg Bolusdosis. Faszikelbildungen in sechs Gebieten des Korpers wurden von 0 bis 3 bewertet und als Gesamt-Faszikelbildungswert summiert. Die Zeiten bis zur ersten Faszikelbildung, Zuckunterdrückung und Tetanusunterdrückung wurden in umgekehrten Bezug zu den Infusionsraten gebracht. Faszikelbildungen in den sechs Gebieten und der Gesamt-Faszikelbildungswert wurden in direkten Bezug zur Infusionsrate gebracht. Die Gesamt-Faszikelbildungswerte in der 30 mg-Bolusgruppe und in den Infusionsgruppen 5 mg s^{-1} und 20 mg s^{-1} waren nicht wesentlich unterschiedlich.

RAPIDEZ DE INFUSION DE SUXAMETONIO Y FASCICULACIONES OBSERVADAS

Un estudio de dosis–respuesta

SUMARIO

Se administro cloruro de suxametonio (Sch) intravenosamente en 36 hombres adultos a seis diferentes velocidades: entre 0,25 mg s^{-1} y 20 mg s^{-1}. La infusión fue suspendida, ya sea cuando cesara la respuesta muscular al estímulo tetánico del nervio ulnar o cuando se excediera 120 mg de Sch. Seis pacientes adicionales recibieron una dosis intravenosa en bolo de 30 mg. Las fasciculaciones en seis sectores del cuerpo fueron clasificadas de 0 a 3 y sumadas para obtener un resultado total de fasciculación. Los tiempos transcurridos hasta la primera fasciculación, supresión de espasmo y supresión del tétanos, estuvieron inversamente relacionados con la rapidez de las infusiones. Las fasciculaciones en los seis sectores y el resultado total de fasciculación estuvieron relacionados directamente con la rapidez de infusión. Los resultados totales de fasciculación en el grupo de bolo de 30 mg en los grupos de infusión de 5 mg s^{-1} y 20 mg s^{-1}, no fueron significativamente diferentes.

Br. J. Anaesth. (1979), **51**, 247

A PAEDIATRIC VENTILATOR WITH A FLUIDIC CONTROL SYSTEM

H. J. MANSON, D. G. ROSS AND C. R. DUNDAS

SUMMARY

A paediatric ventilator has been designed basically as a fluidic-logic controlled T-piece occluder. Inspiratory and expiratory time, inflation pressure limit, positive end-expiratory pressure (PEEP), continuous positive airway pressure (CPAP) and inspiratory flow-rate are controlled independently and intermittent mandatory ventilation (IMV) is available. Warning systems are provided for failure of the driving gas, low airway pressure and inspiratory pressure limit. The breathing circuit is isolated from the control and warning systems for ease of sterilization.

Recently, the design of ventilators for use in paediatric anaesthesia has been based commonly on the intermittent occlusion of the expiratory limb of an Ayre's T-piece circuit. Ward (1975) suggested that, in this situation, fluidic control systems would have certain advantages, not the least of which would be the high degree of reliability conferred by the use of very few moving parts and by the use of the same gas source both as supply to the patient and as power for the ventilator. Accounts of suitable fluidic circuits have been published previously by Meyer and Joyce (1968), Klain and Smith (1976) and Duffin (1977).

MATERIALS AND METHODS

The devices used in the ventilator described in this communication are made by Corning Glass Corporation, Inc., and are known as Fluidic Industrial Control Modules (FICM). Their function is based on the Coanda wall-attachment effect and jet-interaction principles (Conway, 1971). FICM have been available commercially for more than 10 yr and are used widely in industrial control processes. Quality control is high and so far no defective devices have been encountered by the authors. FICM are made by a photographic process from an inert ceramic material, and combine compact size with the extreme reliability in use associated with non-moving-part fluidics, provided the gas supplying them is suitably filtered to exclude small particles.

The time delay relays used in the timing circuit described below do contain moving parts, but in each case these consist of two substantial nitrile rubber diaphragms with a very small range of movement to occlude orifices in smooth ceramic chambers, so their working life is considered in terms of many millions of cycles.

Changes in the viscosity and density of the gas supply affect slightly the function of fluidic-logic devices (Lawler, White and Ross, 1979—in preparation), but in the operating conditions obtaining in this machine these effects are not significant.

The logic circuit used standard FICM attached to a Corning manifold which eliminates many external connections while optimizing interconnection characteristics. The expiratory valve was a standard Bennett balloon-type valve (No. 0563) as used in other ventilators such as the Monaghan 228.

Gauges for airway pressure (P_{AW}) and airway pressure limit (P_{AW} limit) were calibrated (cm H_2O), their controlling restrictors being left uncalibrated, and the restrictors governing the inspiratory and expiratory times used an arbitrary scale.

Power supply and power failure warning

The gas for the patient could be supplied from any conventional apparatus which allows accurate gas mixing and flow control; an example is shown in figure 1. Gas from the supply lines was filtered to 5 μm or less to prevent particle deposition from interfering with reliable function of the fluidics, and passed through check valves which prevented backflow had a pressure difference occurred between the

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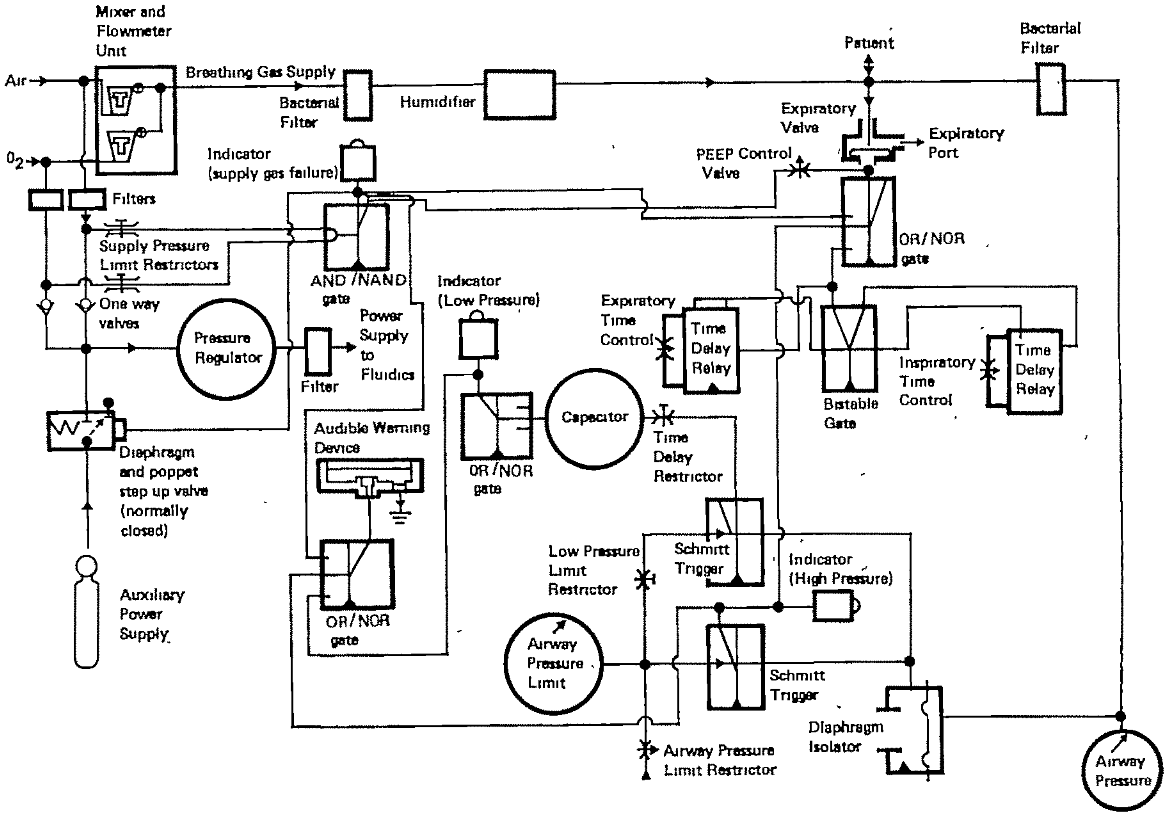

FIG. 1. Paediatric ventilator circuit.

supply lines. The gas passed through a conventional pressure regulator and a final 5-μm filter which removed any particles generated in the check valves and regulator. It formed the power supply to the fluidic components.

Failure of the power supply activated audible and visible alarms as follows: an AND/NAND gate took inputs via preset restrictors from the power lines between the filters and the check valves. Normally the AND output was present, but if either supply pressure decreased below a preset minimum the NAND output appeared, causing a fluidic indicator to change colour and, via an OR/NOR gate, switched on an audible alarm. At the same time an auxiliary gas supply was turned on by means of a diaphragm and poppet valve. Setting up the ventilator *ab initio* on the auxiliary supply was precluded.

This sequence may optionally include prevention of the inspiratory phase (see below). Simultaneously the disappearance of the AND output would cause discontinuation of positive end-expiratory pressure if present.

Control of inspiratory and expiratory time

A bistable amplifier was made to oscillate by means of feedback through two time-delay relays. This arrangement was similar to that used by Klain and Smith (1976) and made it possible to control inspiratory and expiratory time independently. One output of the bistable switched an OR/NOR gate of which the NOR output inflated the balloon-type expiratory valve which occluded the T-piece and caused inspiration.

Airway pressure control and warning systems

Airway pressure was sampled through a bacterial filter, displayed on a manometer and applied to a "diaphragm isolator" which had an analog output and which limited gas flow in the pressure-sensing line to minimize damping effects. The output from the diaphragm isolator formed the input to two Schmitt triggers with linked bias inputs. When airway pressure exceeded the preset airway pressure limit (displayed on a second manometer), one Schmitt trigger switched and simultaneously inhibited inspir-

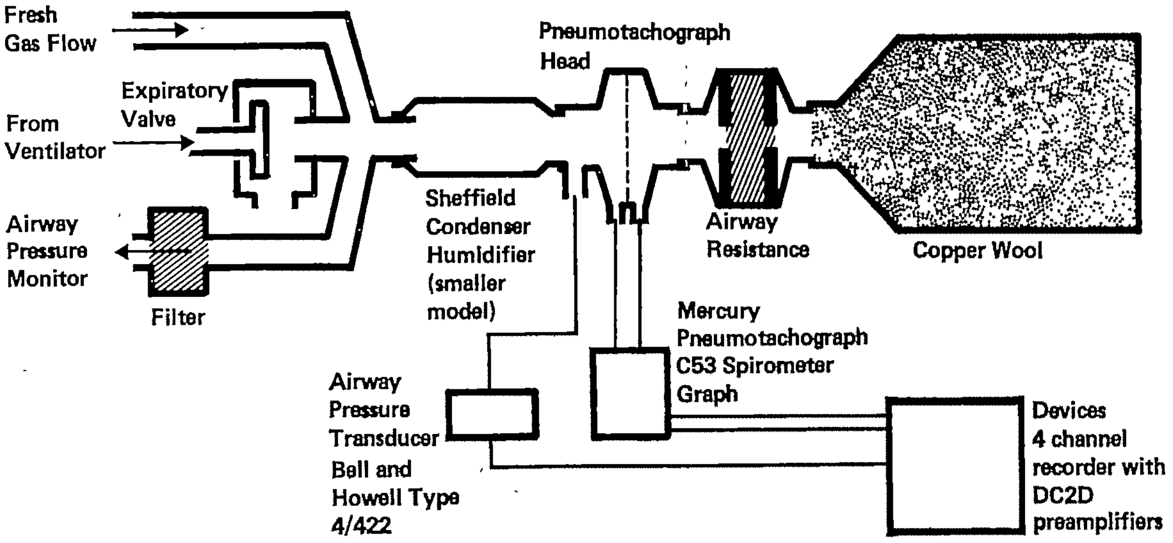
Fresh Gas Flow
From Ventilator
Expiratory Valve
Airway Pressure Monitor
Filter
Pneumotachograph Head
Sheffield Condenser Humidifier (smaller model)
Airway Resistance
Copper Wool
Mercury Pneumotachograph C53 Spirometer Graph
Airway Pressure Transducer Bell and Howell Type 4/422
Devices 4 channel recorder with DC2D preamplifiers

FIG. 2. Test apparatus.

ation, made a visual indicator change colour and sounded an audible alarm. If airway pressure decreased below a certain proportion of the airway pressure limit, this proportion being preset by the low pressure limit restrictor, then the second Schmitt trigger switched an OR/NOR gate to its OR output after a delay of 15 s set by a resistance–capacitance network. The OR output changed the colour of a visual indicator and sounded the audible alarm. However, if airway pressure increased to greater than the lower set limit within the 15-s delay the alarm process was inhibited.

Audible warning device

To conserve gas, the audible warning device was designed to be powered by the output of an OR/NOR gate supplied at only 20.7 kPa. A silicone rubber diaphragm 0.25 mm thick and 2 cm in diameter was stretched across the rim of a cup 6 mm deep. The diaphragm vibrated when gas passed into the cup from the OR output of the OR/NOR gate (fig. 1).

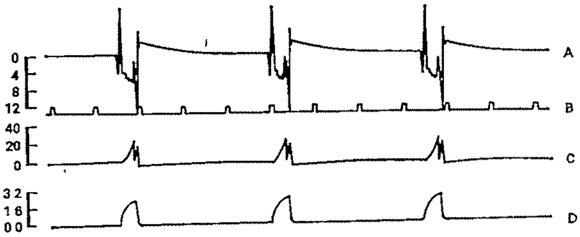

FIG. 3. Ventilator waveforms. Chart speed 2.5 cm s^{-1}, fresh gas flow 6 litre min^{-1}. A = flow (litre min^{-1}); B = time marker; C = volume (ml); D = P_{AW} (kPa).

The ventilator was connected to the test apparatus shown in figure 2. The model lung was constructed as described by Chakrabarti and Sykes (1976), with an internal volume of 3090 ml, an airway resistance of 20 kPa $litre^{-1}$ s^{-1} and a compliance of 29.6 ml

TABLE I. *Maximum fresh gas flow depends on the gas mixing equipment used. PEEP, airway pressure (P_{AW}) limit and low pressure warning-level maxima depend on the setting chosen for their respective restrictors. (See discussion on low pressure warning time delay)*

	Inspiratory time (s)	Expiratory time (s)	Fresh gas flow (litre min^{-1})	PEEP (kPa)	P_{AW} limit (kPa)	Low pressure warning level (kPa)	Time delay on low pressure warning (s)
Max	00	00	30	2	8	2	15
Min	0.35	0.35	0	0	0	0	1

kPa^{-1} measured with the pneumotachograph head in place. The specifications given in table I were verified and some examples of the wave forms produced are shown (fig. 3).

RESULTS AND DISCUSSION

Alternatives existed at several points of the ventilator's design and in the case of two of these the following considerations were taken into account.

The oscillator controlling the times for inspiration and expiration used two time-delay relays which incorporate diaphragms as previously described, but if pure fluid non-moving-part devices had seemed more desirable, the same effect could have been obtained using two Schmitt triggers, at the cost of an increase in gas consumption of 6.5 litre min^{-1} approximately (Ross and Manson, 1979—in preparation). We chose to control the inspiratory and expiratory times independently, as opposed to controlling frequency and inspiratory–expiratory ratio.

The second decision concerned the mode of operation of the ventilator in the case of failure of one or other of the driving gases. Since this machine may be driven by a mixture of gases other than air and oxygen, for example nitrous oxide and oxygen, we chose to have the ventilator stop in expiration with the expiratory valve open should one of the gas supplies have failed. However, it is arguable that if the machine is to operate on air and oxygen it might be better to continue ventilation with whichever gas supply remains. This option would be made available by disconnecting the NAND output of the AND/NAND gate from the input to the OR/NOR gate controlling the expiratory valve.

A further point of interest concerns the operation of the low airway pressure alarm. Since the minimum airway pressure limit was set as a proportion of maximum airway pressure and a time delay was set, PEEP or CPAP could be applied without further controls. Gas consumption of the entire logic circuitry depending on operating circumstances was approximately 30 litre min^{-1}. Consumption of the alarm systems is of the order of 10–12 litre. The ventilator is at present being assessed for commercial production and if it is produced, integrated miniaturized circuitry will be employed. This will reduce the cost of gas to between a quarter and one-half its present level and would decrease eventually the costs of production and make the machine very easy to test and service.

INITIAL CLINICAL EXPERIENCE

The ventilator has been used clinically on five occasions to ventilate the lungs of infants during anaesthesia and has been used also on one occasion in neonatal intensive care. Although clinical experience is restricted so far, the following can be stated. The ventilator was easy to set up and was sensitive and finely adjustable in use. The fact that it operates as a T-piece occluder precluded its use without modification for ventilating any but small infants since, otherwise, the inspiratory flow rate would be insufficient. Some trouble was experienced in the adjustment of the time delay for the low pressure alarm. The restrictor which sets this delay is situated internally and its setting is critical, requiring readjustment on each occasion of use. It is planned to resite the delay adjustment externally and possibly to replace its capacitor–restrictor arrangement with a time-delay relay device.

We intend to subject the machine to more exhaustive clinical testing in the future.

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VENTILATEUR PEDIATRIQUE AVEC SYSTEME A COMMANDE FLUIDIQUE

RESUME

Un ventilateur pédiatrique a été conçu surtout pour l'occlusion de la pièce en T à commande fluidique numérique. Les temps d'inspiration et d'expiration, la limite de la pression d'inflation, la pression positive de fin

d'expiration (PEEP), la pression positive continue dans les passages d'air (CPAP) et le débit inspiratoire sont contrôlés indépendemment, et la ventilation obligatoire intermittente (IMV) y est également disponible. Des systèmes avertisseurs sont prévus en cas de non fonctionnement du gaz d'entraînement, de baisse de pression dans les passages d'air, et de limitation de la pression inspiratoire. Le circuit de respiration est isolé des systèmes de contrôle et des systèmes avertisseurs pour en faciliter la stérilisation.

EIN PÄDIATRISCHER BELÜFTER MIT EINEM FLÜSSIGKEITSREGLERSYSTEM

ZUSAMMENFASSUNG

Der pädiatrische Belüfter wurde im Grunde als ein T-Rahmen-Okkludiergerät mit Flüssigkeits-Logikregelung konstruiert. Ein- und Ausatmungszeit, Aufblasdruckgrenze, positiver Endausatmungsdruck (PEEP), kontinuierlicher positiver Luftwegdruck (CPAP) und Einatmungsrate werden unabhängig voneinander geregelt, und intermittierende obligatorische Belüftung (IMV) steht zur Verfugung. Für Versagen des Treibgases, geringen Luftwegdruck und Einatmungsdruckgrenzen sind Warnsysteme worhanden. Der Atmungskreislauf ist für einfache Sterilisierungsmöglichkeit vom Regler- und vom Warnsystem isoliert.

UN VENTILADOR PEDIATRICO CON SISTEMA DE CONTROL FLUIDICO

SUMARIO

Se ha diseñado un ventilador pediátrico que cumple básicamente la función de ocluidor con pieza en T, controlado por lógica fluídica. El tiempo de inspiración y expiración, límite de presión de inflación, presión positiva al final de la expiración (PEEP), presión positiva continua en las vías respiratorias (CPAP), y rapidez de circulación de inspiración se controlan independientemente y hay disponible ventilación mandataria intermitente (IMV). Se ha equipado con sistemas de advertencia contra fallas del gas impulsor, presión baja en las vías respiratorias y exceso de presión inspiratoria. El circuito de la respiración está aislado de los sistemas de control y advertencia a fin de facilitar la esterilización.

Br. J. Anaesth. (1979), **51**, 253

RECORDINGS OF, AND AN ANATOMICAL EXPLANATION FOR, FALSE POSITIVE LOSS OF RESISTANCE DURING LUMBAR EXTRADURAL ANALGESIA

N. E. SHARROCK

SUMMARY

Loss of resistance dorsal to the ligamentum flavum was recorded in 10 of 16 patients aged 43–75 yr whilst performing extradural anaesthesia at the L2–3 interspace via the midline approach. Degeneration of the interspinous ligament with cavity formation is observed frequently in the elderly and may account for false positive loss of resistance and failure to obtain analgesia following the injection of local anaesthetic.

The induction of extradural analgesia is dependent upon correct positioning of the needle within the extradural space and is aided usually by one of two manoeuvres: the hanging-drop technique of Gutierrez, or the loss of resistance method used originally by Sicard and Forestier and then popularized by Dogliotti (Bromage, 1954). In spite of apparently clear signs, failure to obtain analgesia is not infrequent (Bonica et al., 1957), especially in the elderly (Lund, Cwik and Quinn, 1958). With insertion of the needle via the midline, several authors have noted diminished or "pseudo-loss" of resistance within the interspinous ligament (Bromage, 1954; Moore, 1965; Davidson, 1966), and others false positive hanging-drop signs while the needle was still within the interspinous ligament (Figueiredo, 1948; Bromage, 1954; Fleming and Campbell, 1959). Cavity formation within the interspinous ligament has been described (Rissanen, 1960, 1962) and may thus obscure location of the extradural space and account for many of the failed lumbar extradural blocks performed using the midline approach.

METHODS

To document the loss of resistance within the interspinous ligament, 16 patients aged 43–75 yr and undergoing extradural anaesthesia were studied. A 17-gauge Tuohy needle was inserted 1–2 cm into the interspinous ligament via the midline approach at the L2–3 interspace and the stylet was withdrawn. A four-way stop cock, connected via saline-filled tubing to a pressure transducer, was interposed between a 2-ml glass syringe and the Tuohy needle. Pressures within the air-filled syringe were recorded while testing manually for loss of resistance after each advancement of the needle. Correct location of the needle in the extradural space was verified ultimately by the production of successful analgesia.

RESULTS

Tracings from six representative patients are shown in figures 1–3. Six of the 16 patients studied had uniformly consistent interspinous ligaments with continued resistance to the injection of air until the extradural space was entered (fig. 1). In the other 10 patients, loss of resistance was detected more superficially than anticipated (figs 2 and 3). In five patients there was partial loss of resistance in contrast to the more complete lack of resistance observed when the extradural space was entered (fig. 2). On the other hand, in five patients complete loss of resistance was recorded within the interspinous ligament and could not be differentiated from that observed after the needle had pierced the ligamentum flavum and entered the extradural space (fig. 3). The pressure patterns observed when injecting air into the extradural space varied (figs 1–4) to such an extent that the interspinous ligaments of certain patients (male, 64 yr; male, 68 yr; male, 63 yr) appeared more compliant than the extradural space of others (male, 58 yr; male, 46 yr; male, 64 yr).

Two patients are presented in whom there was difficulty in locating the extradural space.

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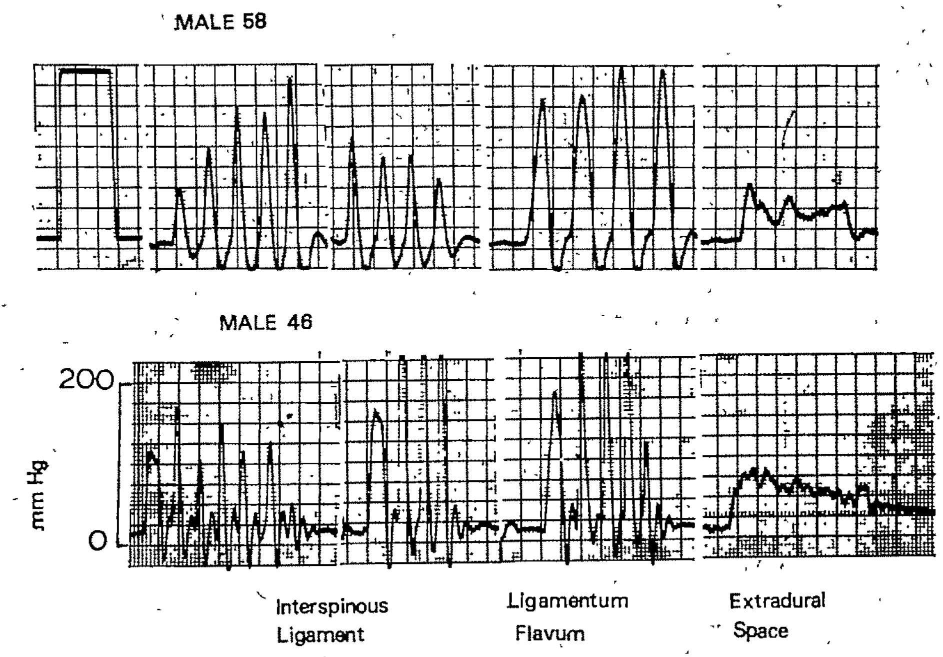

FIG. 1. Pressure recorded while testing manually for loss of resistance, demonstrating a consistent interspinous ligament. (Paper speed 5 mm s^{-1}.)

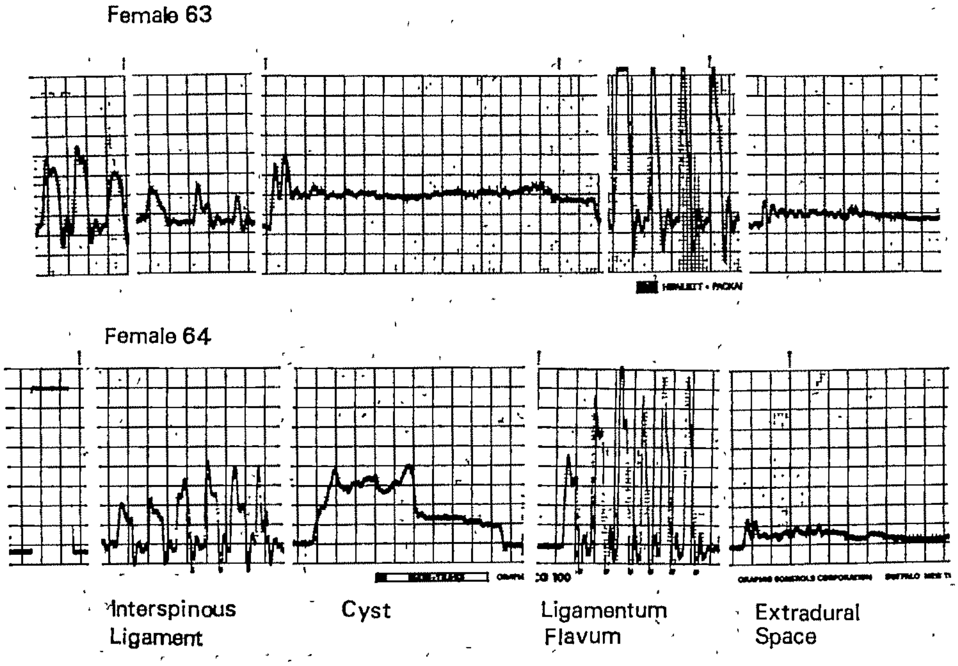

FIG. 2. Pressure recorded while testing manually for loss of resistance, demonstrating "pseudo-loss" of resistance.

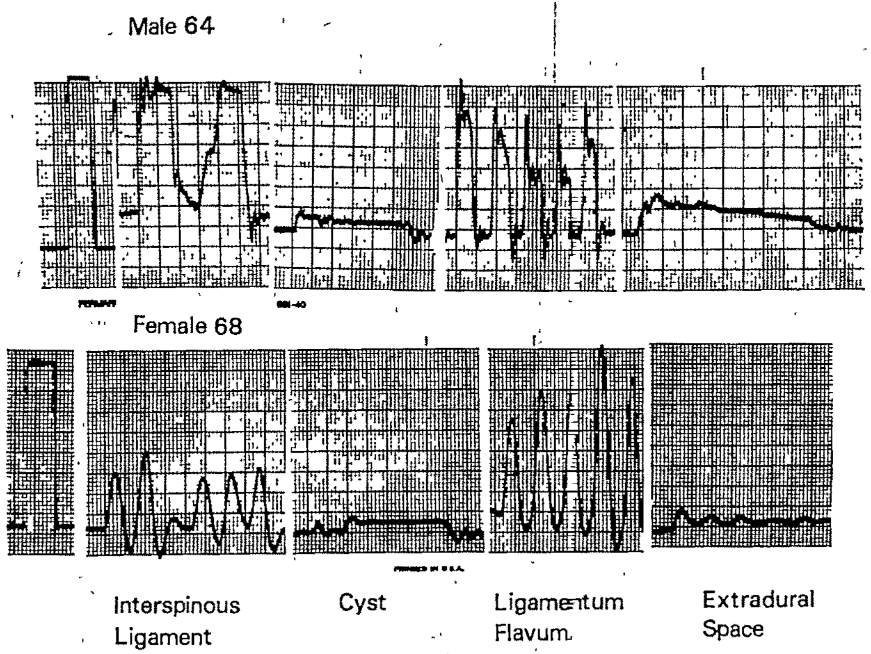

FIG. 3. Pressure recorded while testing manually for loss of resistance, demonstrating complete loss of resistance within the interspinous ligament superficial to the ligamentum flavum.

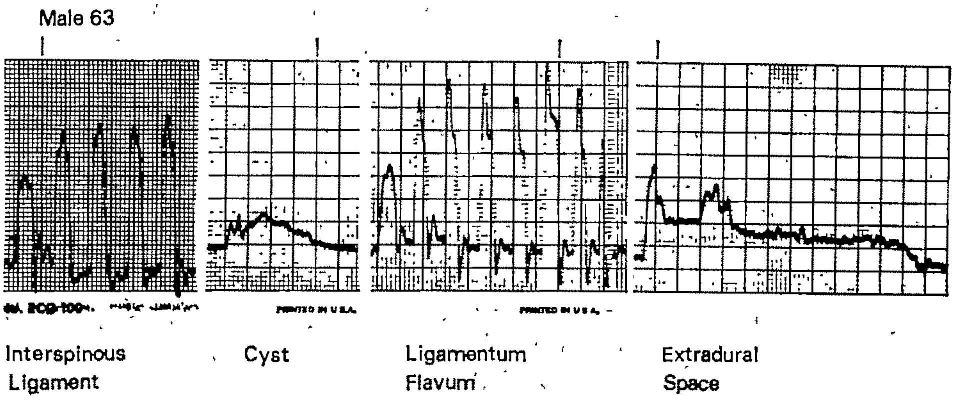

FIG. 4. Pressure recording demonstrating loss of resistance within the interspinous ligament in a patient who received a failed extradural injection (L2–3).

Patient 1

A male, aged 60 yr, height 185 cm was to have a femoro–popliteal arterial bypass graft under extradural analgesia. Loss of resistance was obtained at a depth of 6.5 cm from the skin using a 17-gauge Tuohy needle which had been inserted in the midline at the L2–3 interspace. Seventeen millilitre of bupivacaine 0.75% was injected with ease, yet no analgesia developed after 30 min. General endotracheal anaesthesia was instituted. The patient returned 1 yr later for an ileofemoral arterial bypass graft. An extradural block was performed at the L2–3 interspace via the midline with the aid of the pressure transducer technique described. The tracing is shown in figure 4. Appreciable loss of resistance was observed at approximately 6 cm from the skin, but resistance returned at 7 cm. Subsequent loss of resistance was noted at a depth of approximately 7.5 cm. Successful analgesia to T4 developed within 15 min after injection of 15 ml of bupivacaine 0.75%.

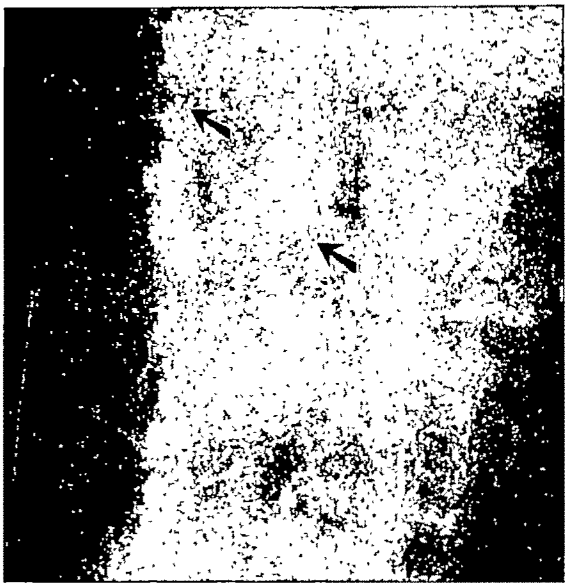

FIG. 5. Lateral x-ray of the upper lumbar spine demonstrating a catheter within the extradural space (lower arrow) whereas the upper is dorsal to the lamina.

Patient 2

A 64-yr-old male, height 175 cm, was to undergo resection of an abdominal aortic aneurysm under extradural analgesia. A 17-gauge Tuohy needle was inserted into the L1–2 interspace via a midline approach with the patient in the lateral decubitus position, using an air-filled glass syringe to detect loss of resistance. The ligament appeared firm until definite loss of resistance was noted 6.5 cm beneath the skin. Eighteen millilitre of 0.75% bupivacaine was injected with ease, but the catheter could not be advanced beyond the needle tip. Thirty minutes later there had been no change in arterial pressure and no sign of analgesia. The patient was repositioned and a 17-gauge Tuohy needle re-introduced at L2–3. "Pseudo-loss of resistance" was detected throughout the interspinous ligament, but at a depth of 7 cm, additional resistance to injection of air was detected. The needle was advanced further, a definite "give" detected and loss of resistance obtained again. Fifteen millilitre of bupivacaine 0.75% was injected, a catheter was passed 2 cm beyond the needle tip and, within 10 min, analgesia to T4 had developed.

After operation each catheter was filled with contrast medium 0.4 ml and a lateral x-ray of the lumbar spine was taken with the patient supine. The lower catheter was seen to be present in the extradural space, whereas the upper catheter tip lay dorsal to the lamina (fig. 5).

DISCUSSION

Loss of resistance may occur superficial to the extradural space if the needle deviates from the midline and enters the paravertebral muscles (Bonica, 1956).

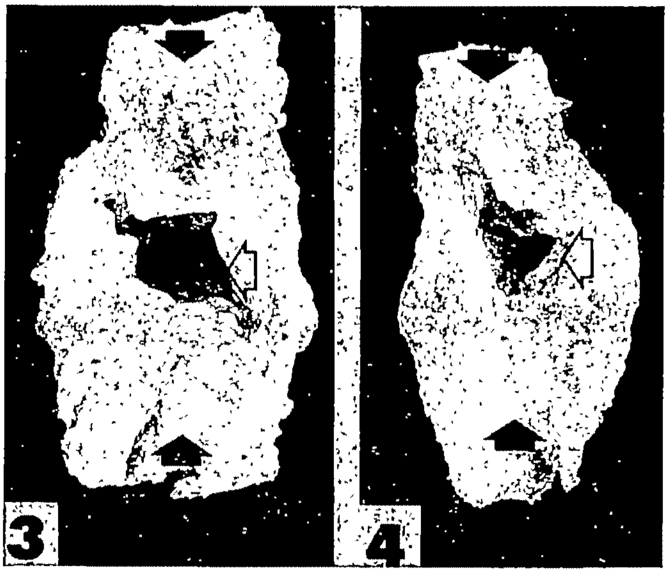

FIG. 6. Coronal section through the L4–5 interspinous ligament demonstrating cavitation. Solid arrows depict L4 and L5 spines, open arrows lateral margins of the cyst. Reproduced with permission from Dr Rissanen (Rissanen, 1960).

Thus it is possible that the false positive loss of resistance observed in this study reflected needle entry to paravertebral tissues. However, the loss of resistance was always detected in the midline, with the needle presumably still within the interspinous ligament. Furthermore, degeneration of the interspinous ligament with resultant cavity formation is frequent in elderly patients (fig. 6) (Rissanen, 1962) and needle entry into such a cavity probably accounts for most of the instances of false positive loss of resistance.

Cysts usually occur between L5–S1 and L4–5 spines, less commonly between L2–3 and are unusual between T12 and L1. The largest cysts are observed in the elderly, particularly in the lower lumbar interspaces. Degeneration occurs initially in the centre of the ligament and, with ageing, cavitation results with formation of a mesothelial lining. Thus the cyst creates a pseudo-joint between adjacent surfaces of the vertebral spines (Rissanen, 1962). At necropsy 85% of subjects aged 61–79 yr had interspinous cyst formation in the lumbar region. In the young cavitation is usually less extensive, but may be prominent especially in the L5–S1, L4–5 interspaces (Rissanen, 1960). These changes are not found at ages less than 20 yr, but become more frequent with age or in association with intervertebral disc proplase, pronounced lumbar lordosis and Paget's disease (Rissanen, 1962). Cavitation of the interspinous ligament is usually asymptomatic and radiologically there is no sign of cyst formation, although "kissing spines" which are associated with interspinous cavitation have been detected in 27% of adults by x-ray (Rissanen, 1960). Typically, the lumbar spines are close together with sclerosis of the opposing margins, while in the anteroposterior projection, transverse, and sometimes oblique facet formation of the spines is seen (Epstein, 1969).

A sudden loss of resistance may be encountered upon entering one of these cysts. If it is large there may be little resistance on injection as the lateral walls of the interspinous ligament expand accommodating 15–20 ml with ease (as in patients 1 and 2). A lesser loss of resistance will occur in a smaller cavity, making injection of local anaesthetic difficult. If a large pseudoarthrosis is entered close to the ligamentum flavum and loss of resistance detected, the temptation is to assume that the needle has entered the extradural space and to inject the local anaesthetic. This probably accounts for many failed extradural blocks while using the loss of resistance technique.

Failure to obtain analgesia may occur also in spite of a positive hanging-drop sign (Bromage, 1954; Fleming and Campbell, 1959; Rissanen, 1962). Figueiredo (1948) considered that this was the result of creating a vacuum as the needle was withdrawn after contacting bone, but Bromage (1954) attributed failure to movement of the patient. On the other hand, flexion of the spine may enlarge a cyst and create a vacuum, thereby causing inward movement of a hanging drop as the needle enters the cavity (fig. 7). With lesser flexion no vacuum is generated and the hanging drop will not move.

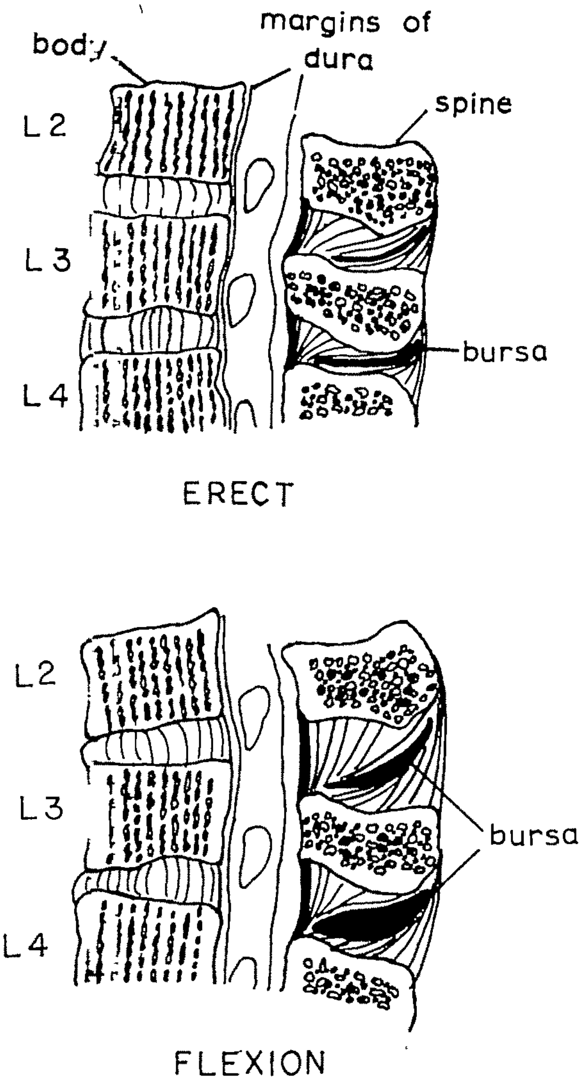

FIG. 7. Diagram of a sagittal section of the lumbar spine to demonstrate the potential enlargement of a cyst during flexion.

It may be impossible to distinguish between a cyst and the extradural space, especially if a cyst is entered close to the ligamentum flavum. If the needle is considered too superficial to be in the extradural space when loss of resistance develops, it may be advanced to the ligamentum flavum where resistance to the injection of air will be obtained again (Moore, 1965). The subsequent loss of resistance observed when the needle pierces the ligamentum flavum verifies successful extradural entry (Moore, 1965) (figs 2–4). However, this technique is unsatisfactory because a high frequency of subarachnoid taps may result if this potentially ambiguous sign is used. Moore (1965) advocates inserting the needle well into the interspinous ligament so that the needle point is within or near the ligamentum flavum before testing for loss of resistance. This can be misleading also as the needle may still be within a cyst or have transversed the ligamentum flavum to be within the extradural space or c.s.f. if these structures are more superficial than anticipated. On the other hand, the lateral approach may be more reliable, particularly in elderly patients, as it provides assurance that the extradural space will be entered when the needle is advanced several millimetres beyond the rostral edge of the lamina. However, in younger patients, the midline approach can be very reliable (Hehre, Sayig and Lowman, 1960) as interspinous ligament cysts are less frequent and smaller than in older individuals (Rissanen, 1960, 1962).

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ENREGISTREMENTS ET EXPLICATION ANATOMIQUE D'UNE FAUSSE PERTE POSITIVE DE RESISTANCE PENDANT UNE ANALGESIE LOMBAIRE EXTRADURALE

RESUME

On a enregistré sur 10 patients (sur un total de 16) âgés de 43 à 75 ans, une perte de résistance au dos des ligaments jaunes alors que l'on procédait à une anesthésie extradurale dans l'espace intervertebral L.2–3 par la voie médiane. On observe fréquemment chez les personnes âgées, une dégénérescence du ligament interspinal avec formation de cavité; ceci pourrait être la raison de la fausse perte positive de résistance, et de l'absence d'analgésie après l'injection d'un agent anesthésique local.

AUFZEICHNUNGEN VON, UND EINE ANATOMISCHE ERKLÄRUNG FÜR, FALSCHEN POSITIVEN WIDERSTANDSVERLUST WÄHREND LUMBARER, EXTRADURALER ANALGESIE

ZUSAMMENFASSUNG

Verlust des Widerstandes dorsal zum Ligamentum flavum wurde bei 10 von 16 Patienten im Alter zwischen 43 und 75 Jahren aufgezeichnet, während eine extradurale Anästhesie im L2–3-Zwischenraum von der Mittellinie aus vorgenommen wurde. Degeneration des interspinalen Gewebes sowie Hohlenbildung wird bei älteren Patienten häufig beobachtet, was zu einem falschen positiven Widerstandsverlust führen kann und dazu, dass nach Vornahme der Lokalanasthesie keine Analgesie erzielt werden kann.

REGISTRO Y EXPLICACION ANATOMICA DE LA PERDIDA DE RESISTENCIA POSITIVA FALSA DURANTE ANALGESIA EXTRADURAL LUMBAR

SUMARIO

Se registró una pérdida de resistencia, dorsal al ligamento amarillo, en 10 de 16 pacientes cuyas edades fluctuaban entre 43 y 75 años, durante anestesia extradural en el espacio intermedio L2–3, administrada por vía del acceso de línea media. En las personas de edad avanzada se observa con frecuencia una degeneración del ligamento interespinal y la formación de una cavidad, lo que podría explicar la pérdida de resistencia positiva falsa e incapadciad de recibir analgesia tras la inyección de anestesia local.

Br. J. Anaesth. (1979), 51, 259

BEDSIDE ANGIOGRAPHY OF THE LUNG BY SWAN–GANZ CATHETER

A case report

J. J. DE LANGE, L. G. THIJS AND C. PEARCE

SUMMARY

A Swan–Ganz catheter, employed for haemodynamic monitoring, was put to a use not described previously. Pulmonary angiography was performed through the catheter at the bedside with minimal discomfort or complication. In this case it was possible to determine that a lung abscess was responsible for a translucency in the right lower lobe. This was subsequently confirmed at postmortem examination.

Swan and co-workers (1970) described a balloon catheter for measuring pulmonary artery pressure which could be inserted and placed accurately without using x-ray fluoroscopy.

Subsequently, new applications for this catheter have been described:

(a) Bedside measurement of cardiac output using the principle of thermodilution (Ganz and Swan, 1972).

(b) Pulmonary arterial blood sampling for measuring intrapulmonary shunting. Smith and others (1973) have shown that, particularly in patients with acute pulmonary disease, better results are obtained with pulmonary artery than with vena cava blood.

(c) Selective angiography, particularly for localization of emboli (McIntyre and Sharma, 1974; Wilson and Bynum, 1976).

There has been no report published of bedside angiography through a previously inserted Swan–Ganz catheter. In the following report this particular application is described.

CASE REPORT

A 24-yr-old female was admitted to our hospital on April 28, 1977 on account of progressive cardiac failure. She had been in excellent health before December 1976 when she developed tonsillitis and pharyngitis. There were progressive symptoms of malaise, dyspnoea, tachycardia, increase in weight and intermittent fever.

On physical examination the patient appeared ill. Temperature was 37.5 °C, heart rate 120 beat min^{-1}, regular and thready, arterial pressure 100/80 mm Hg; central venous pressure 20 cm H_2O. The heart was enlarged but no murmurs were heard. Pitting oedema was present in the ankles. The extremities were cyanosed. Chest x-ray confirmed cardiomegaly, the lungs showing mild pulmonary venous engorgement. The e.c.g. showed sinus tachycardia with nonspecific ST-T changes and echocardiography showed only a dilated left ventricle.

Laboratory studies showed mild disturbance of renal and hepatic function and definite disseminated intravascular coagulation. Extensive investigation, including bacteriological, virological, immunological and pathological tests showed only one definite abnormality. The titre of the complement fixation test for herpes simplex antibodies increased from 1 : 32 to 1 : 256, although herpes simplex virus could not be isolated.

A presumptive diagnosis of cardiomyopathy or myocarditis was made and treatment commenced with diuretics and digitalis. The patient's general condition gradually improved. On July 6, however, the patient's condition deteriorated suddenly, with right-sided chest pain, dyspnoea and shock. The clinical diagnosis of pulmonary embolism was supported by a lung perfusion scan. Treatment with heparin was started.

Artificial ventilation of the lungs was necessary to maintain acceptable arterial gas tensions. Circulatory indices, however, did not improve and a Swan–Ganz catheter was inserted via the right femoral vein. At this stage a cavity-like structure in the region of the right lower lobe became visible on the chest x-ray (fig. 1). The differential diagnosis was gas in the colon, normal lung tissue, air under the diaphragm, and a lung bulla and abscess. Arteriography of this area was performed via the Swan–Ganz catheter, the

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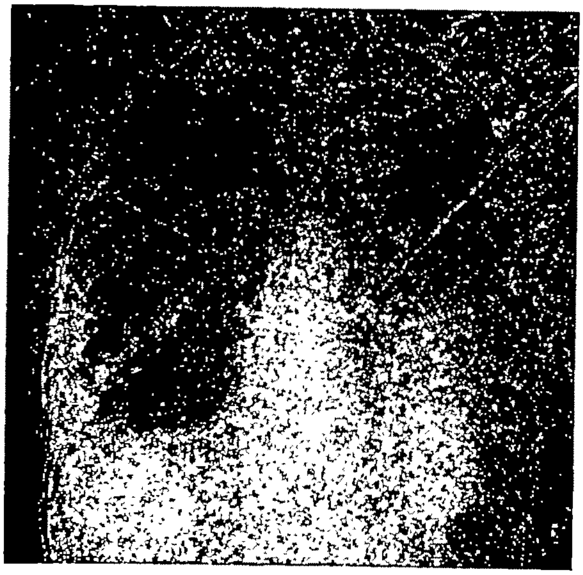

FIG. 1. Chest x-ray with a cavity-like structure in the right lower lobe.

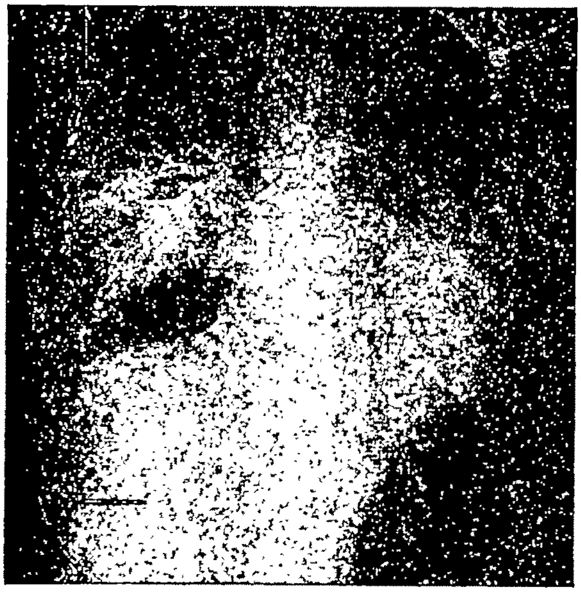

FIG. 2. Arteriogram via the Swan–Ganz catheter *in situ*, which supported the diagnosis of lung abscess.

result supporting the diagnosis of lung abscess (fig. 2).

Despite intensive therapeutic efforts the patient died on July 28, 1977, in cardiorespiratory failure.

At autopsy non-specific diffuse myocarditis was found with large thrombi in the left ventricle and right atrium. A large lung abscess on the basis of an old lung infarction was present in the right lower lobe. Viral culture was negative so that the aetiology of the myocarditis was never determined.

DISCUSSION

This report demonstrates a further diagnostic possibility in patients with Swan–Ganz catheters *in situ* for haemodynamic monitoring.

The whole procedure can be performed simply at the bedside. After inflating the balloon to the volume necessary to obtain a typical wedge-pressure curve, 5–10 ml of a suitable contrast agent (we used Conray 70) at body temperature is injected through the catheter and chest x-ray is taken.

Our animal experiments (de Lange and Stamenković, 1979) show that the procedure is no more dangerous than a chest x-ray provided there is no hypersensitivity or allergy to the contrast agent.

One limitation is that it is possible to make angiograms only of one lung or part of one lung. Placement in other regions requires manipulation of the catheter which carries the risk of infection and necessitates bedside fluoroscopy.

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ANGIOGRAPHIE DU POUMON EFFECTUEE AU CHEVET A L'AIDE DU CATHETER DE SWAN-GANZ

Rapport sur un cas précis

RESUME

Un cathéter de Swan-Ganz, utilisé pour la surveillance hémodynamique a été employé pour un usage qui n'avait pas encore été décrit. On a effectué une angiographie

pulmonaire au chevet à travers le cathéter, avec un minimum de douleurs ou de complications. Dans ce cas, il a été possible de déterminer qu'un abscès du poumon était responsable d'une translucidité dans le lobe inférieur droit. Ceci a par la suite été confirmé lors de l'autopsie.

ANGIOGRAPHIE DER LUNGE MIT EINEM SWAN-GANZ-KATHETER AM KRANKENBETT

Ein Krankenbericht

ZUSAMMENFASSUNG

Ein Swan-Ganz-Katheter, gewöhnlich zur Überwachung der Hämodynamik benutzt, wurde in einer bisher noch nicht beschriebenen Weise angewant. Lungenangiographie wurde mit diesem Katheter am Krankenbett ausgeführt, dabei nur geringes Unbehagen oder Komplikationen verursachend. In diesem Fall war es möglich, festzustellen, dass ein Lungenabszess an einem Durchscheinen im rechten unteren Lungenlappen Schuld war. Dies wurde spater bei der Autopsie als richtig bestatigt.

ANGIOGRAFIA EN CAMA DEL PULMON EMPLEANDO UNA SONDA SWAN-GANZ

Informe de un caso

SUMARIO

Una sonda Swan-Ganz, empleada habitualmente para el control hemodinámico, fue utilizada para un fin no descrito anteriormente. Se realizó una angiografía pulmonar ampleándose la sonda, estando el paciente en cama y sufriendo éste un mínimo de incomodidad y complicaciones. En este caso fue posible determinar que una traslucidez en el lóbulo inferior derecho se debía a un absceso en el pulmón. Esto fue confirmado posteriormente en la autopsia.

Br. J. Anaesth. (1979), **51**, 263

CORRESPONDENCE

VALVULAR GLOTTIC OBSTRUCTION IN A BABY

Sir,—Twelve days before admission, a baby girl (aged 9 months, wt 12 kg) had coughed violently while eating boiled egg and bread and, although it was considered possible that she had aspirated some food, she had remained well for 8 h until severe dyspnoea developed during sleep. An initial diagnosis of asthmatic bronchitis was made and she was treated with isoprenaline and bromhexine.

On the day of her emergency admission to the paediatric clinic of our hospital, she had suddenly developed severe dyspnoea with inspiratory stridor, and cyanosis. Shortly after admission, bronchoscopy was performed using a 3-mm bronchoscope under general anaesthesia comprising 50% nitrous oxide in oxygen with halothane 1–4%. Bronchoscopy revealed a foreign body lodged directly below the vocal cords. This was white in colour and it moved upwards and downwards with respiration, completely obstructing the larynx during inspiration. After removal, the object was seen to be a fragment of egg shell with a roughened circumference and surface area of $0.5\ cm^2$. A second smaller fragment of eggshell was removed from the orifice of the left main bronchus. Further examination of the bronchial tree revealed no abnormality. Cardiac and respiratory rates were monitored using two stethoscopes during the 45-min procedure; atropine 0.3 mg was administered i.v. when a reduction in heart rate from 130 beat min^{-1} to 90 beat min^{-1} was detected. After operation, steroid and antibiotic therapy were given, and the baby made a good recovery.

Many types of foreign material have been recovered from the respiratory tract during bronchoscopy in children; this presentation is unusual in that the onset of severe airway obstruction was delayed for 12 days, when the larger piece of eggshell caused a valve-like obstruction at the level of the vocal cords.

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CHLORAZEPATE FOR PREMEDICATION

Sir,—I would like to make the following observations on the article by Cohen and others (1978) on the use of chlorazepate for premedication on the night before operation.

Although the results obtained were submitted to Student's *t* test, I feel that this may not be valid without modification. More than one-third of the patients entering the prospective trial were excluded because either the proposed operation was cancelled or insufficient data were collected. However, the number excluded in the placebo group (15/30) was significantly greater (χ^2 test $P < 0.05$) than the number in the treated group (6/30). A further group of the patients was excluded from the final evaluation following full recovery from anaesthesia, but no reason was given. This included more than one-half of the patients receiving the drug although the authors claim no complications were encountered. Had these patients fled the theatres in terror? No indication is given that allowance is made in the statistical analysis for the missing two-thirds of the results.

I feel that, while the manufacturers may derive satisfaction that the drug they market as a tranquillizer does appear effective in the face of a known anxiety-causing stimulus (surgery), the advantage of such a long-acting drug (mean half-life 53 ± 6 h) is obscure. Since the patient receiving the placebo had the same anxiety scores as the treated patients immediately after recovering from anaesthesia, as assessed by the authors' chart (which, incidentally, is a table of values, not a nomogram as stated), I see no reason for giving a drug which continues to act for a further 2 days. The manufacturers issue the same cautions for this drug as for all other benzodiazepines.

Since the trial was not a comparison with any other accepted premedication regimen, but rather a test of anxiolysis, I am unlikely to use chlorazepate. In addition, the authors advocate the use of an opiate where necessary, and so I shall continue to prescribe papaveretum and hyoscine.

D. E. Jeal
London

REFERENCE

Cohen, A. R., Levin, A., Houlton, P. J. C., and Wolhuter, A. (1978). The use of chlorazepate for premedication on the night before surgery. *Br. J. Anaesth.*, **50**, 821.

Sir,—We are grateful to Dr Jeal for his comments regarding our recent paper and for the opportunity to reply.

Dr Jeal is correct in stating that significantly more patients were excluded from the placebo group. However, this fact was related to the availability or otherwise of our psychiatric colleagues and depended on the demands of their considerable and sometimes unpredictable clinical work load. Thus, these exclusions occurred on a purely random, and therefore, unbiased basis and as such are unlikely to have influenced the results of the trail. We could have avoided this criticism by stating that 15 patients were included in the placebo group and 24 in the drug group.

Several patients were missed in the final evaluation, again owing to pressure of work on our psychiatrists. None of our patients "fled the theatre in terror", indeed, perhaps the opposite was true in that the prolonged interview the night before surgery could only serve to reinforce patient rapport with, and confidence in, the anaesthetist.

We acknowledge Dr Jeal's strict interpretation of the word nomogram, in which he is correct.

In the final analysis, Dr Jeal is entitled to his preference for papaveretum and hyoscine, but some anaesthetists might perhaps be seeking a better drug combination to improve patient comfort and welfare. It is these specialists whom we hope to interest in the results of this basic clinical trial of chlorazepate.

A. R. Cohen
Durban, S. Africa

CALIBRATION OF A METHOXYFLURANE VAPORIZER FOR TRICHLOROETHYLENE

Sir,—As methoxyflurane is a very potent anaesthetic, it is administered routinely from vaporizers specifically designed and calibrated for its use (e.g. Cyprane Pentec, Foregger Pentomatic). The recognition of the nephrotoxicity of methoxyflurane has resulted in a decline in its usage, thereby putting out of use a substantial number of vaporizers. Conversion of these unused vaporizers for use with an alternative anaesthetic agent would be economically advantageous.

The ideal alternative anaesthetic should have physical properties similar to those of methoxyflurane. Of all the volatile agents, only trichloroethylene has physical properties similar to those of methoxyflurane (Dorsch, 1975). At 18 °C, the corresponding vapour pressures are 23 mm Hg for methoxyflurane and 60 mm Hg for trichloroethylene. Substitution of trichloroethylene for methoxyflurane should result, therefore, in an output nearly threefold greater than the indicated dial concentration. Furthermore, the change in vapour pressure with temperature for the two anaesthetics is linear throughout the range of ambient temperatures. Were the vapor pressures nonlinear, the trichloroethylene output would vary with changing ambient temperature from a temperature-compensated methoxyflurane vaporizer. Lastly, the anaesthetic potencies for both agents are virtually identical (Wylie, 1972).

The concentrations of trichloroethylene delivered from a Cyprane Mark I Pentec were measured by gas chromatography using a trichloroethylene standard (obtained from Liquid Carbonic) as a reference. The temperature of the vaporizer was maintained constant by partially submerging the unit in a temperature-controlled water bath. Determinations were performed with an oxygen flow rate of 6 litre min^{-1} at 20 °C. It was apparent that trichloroethylene could be vaporized in a predictable fashion using the methoxyflurane vaporizer (fig. 1). The output of trichloroethylene ranged from an initial value of 0.45% to a maximum of 4.8% and, as predicted, the trichloroethylene output was approximately three times the dial setting (fig. 1).

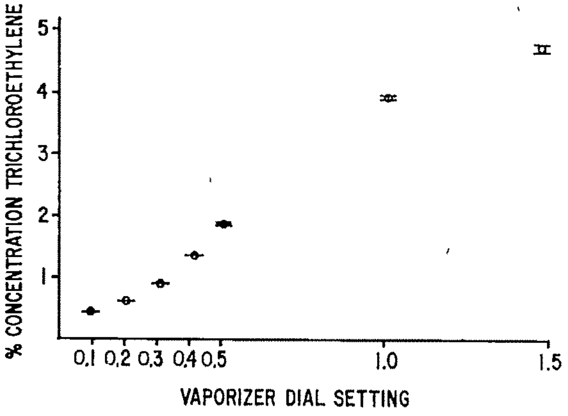

FIG. 1. Concentrations of trichloroethylene delivered from a Cyprane Mark 1 methoxyflurane vaporizer with an oxygen flow rate of 6 litre min^{-1} at 20 °C. Each point represents the mean of three determinations ±1 SD.

The use of trichloroethylene may be debatable in view of the current controversy associated with this agent, based on its alleged carcinogenicity (NCI, 1976). Also, the upper range of trichloroethylene delivered with this vaporizer is much greater than safe clinical concentrations (Lee, 1968). If a methoxyflurane vaporizer is used to vaporize trichloroethylene, it is imperative that the following precautions be taken:

(a) The vaporizer should be clearly labelled to indicate that it is vaporizing trichloroethylene and not methoxyflurane.
(b) The anaesthetist should be aware of the performance characteristics of the methoxyflurane vaporizer with trichloroethylene.
(c) The dial of the methoxyflurane vaporizer should have a mechanical stop immediately following the 0.4% setting to prohibit the administration of trichloroethylene in concentrations exceeding 1.5%.

With these stipulations, one should be able to use such a modified vaporizer to administer trichloroethylene safely and effectively.[†]

R. M. ROSENBLATT
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California, U.S.A.

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USE OF NEOSTIGMINE AFTER SNAKE BITE

Sir,—We feel that the paper by Naphade and Shetti (1977) does not reflect modern concepts in the management of snake bite. The opening sentence "Snakes and cretes are found all over the world . . ." fails to define "cretes", and the summary begins with "Cobra venom consists of neurotoxin which is . . .", but in the text the authors mention 11 distinct entities known to be in cobra venom.

The writers ignore the principles of management of snake bite which have been established over many years and are summarized by a number of workers such as Reid (1971), Minton (1974) and Sutherland (1975, 1976). These principles consist of:

(1) Immobilization of the bitten limb.
(2) Strict rest—the victim should not be permitted to walk.
(3) Application of an appropriate firm roller bandage—an arterial tourniquet is not necessary to prevent absorption of venom through lymphatics.
(4) The only specific life-saving therapy is the appropriate antivenom infused promptly in the correct dosage if significant envenomation has occurred.

If the venom is inadequately neutralized then a number of complications may arise. In the modern literature cryotherapy is considered to be of little value in the treatment of elapid bites (Minton, 1974). In Australia many hundreds of snake-bite victims are treated successfully with antivenom every year. Artificial ventilation is necessary only if antivenom has been delayed unduly. Deaths from snake bite in Australia in recent years have all resulted from failure to administer antivenom, or from an inadequate dose of antivenom or the use of the wrong antivenom (Sutherland, 1977). Pleas have been made in editorials for the better management of snake bite (Editorial, 1975; Editorial, 1978).

In their paper, Naphade and Shetti do not disclose the species of snake, give details of the source, specificity, quantity or potency of the antivenom, or state when antivenom was given and how much later the neostigmine was administered. This lack of information implies that the writers doubt the efficacy of antivenom, yet they list in detail a number of dangerous venom components it is known to neutralize. Since antivenom was given there is no evidence to show that this was not the cause of the child's improvement.

They present no evidence that antivenom is responsible for the neuromuscular block, rather than the neurotoxins.

We believe that neostigmine might be of slight help in the minority of snake-bite cases after adequate treatment with antivenom. Neostigmine will not improve victims of the bite of snakes of which the venom has potent neurotoxins which act presynaptically. A number of the most dangerous snake venoms have been found to be predominantly presynaptic in action, and these include the Asian krait (*Bungaris multicinctus*), the Australian tiger snake (*Notechis scutatus*) and the taipan (*Oxyuranus scutellatus*). There is no place for the use of neostigmine in the management of snake bite in Australia. We believe it has not been demonstrated to be of use in the treatment of snake bite in other countries.

Tess Brophy
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DENTAL ANAESTHESIA

Sir,—Having read Dr Scurr's letter (1978) relating to improvements to training schemes for dental anaesthesia and sedation in the United Kingdom, I thought your readers may be interested to know of some recent developments in Australia.

In November 1975, the Health Commission of New South Wales appointed a committee to investigate the use of relative analgesia, i.v. sedation and general anaesthesia in dental practice. Its report (Wright et al., 1978) contains many recommendations including the establishment of a Department of Clinical Pharmacology and Anaesthesia within the Faculty of Dentistry at Sydney University. The Committee has accepted that the usage of relative analgesia, i.v. sedation and general anaesthesia is part of the present-day practice of dentistry, and it has recommended that dentists who wish to include general anaesthesia in their clinical practice should be given the opportunity to complete a suitable course of instruction which would include residency at a major teaching hospital.

The Australian Society for the Advancement of Anaesthesia and Sedation in Dentistry (A.S.A.A.S.D.) will commence an entirely new teaching programme in 1979 which is designed to equip general dental practitioners with the necessary skills to use safe, simple techniques. The programme consists of six units of instruction and each candidate will be required to:

(a) complete each unit in its correct order;
(b) work for one year with a recognized practitioner;
(c) be evaluated by a review committee at the completion of the programme.

This programme has been approved by the Australian Dental Association, the Faculty of Anaesthetists of the Royal Australasian College of Surgeons and the Oral Surgeons Society of N.S.W. Full details of this new programme were published recently (Sheridan et al., 1978) and further information can be obtained by writing to me.

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HYPERSENSITIVITY TO ATROPINE

Sir,—With reference to the letter of Dundee and Mirakhur (1978), it is worth pointing out that glycopyrronium is not yet available in Greece.

Some months ago, a 4-yr-old baby boy of 18 kg body weight had to undergo an operation for congenital cataract. Allergy to atropine—mentioned by his parents—was proved by testing with atropine 1 : 1 000 000. The anaesthetic management comprised premedication with droperidol

1.6 mg and fentanyl 0.03 mg 45 min before surgery, and anaesthesia was induced with ketamine 50 mg. Endotracheal intubation was facilitated with suxamethonium 20 mg i.v. Anaesthesia was maintained with nitrous oxide in oxygen 2 : 1 and ventilation was controlled with pancuronium 1.5 mg. The neuromuscular blockade was antagonized by hyoscine 0.2 mg and neostigmine 1 mg i.v.

Arterial pressure was maintained at 110/80 mm Hg and the heart rate at 120 beat min^{-1} until the injection of hyoscine which increased the rate to 160 beat min^{-1}. This effect lasted for about 5 min until the neostigmine produced a gradual reduction of heart beat to 68 beat min^{-1}, and 30 min later the heart rate remained stable at 100 beat min^{-1}.

M. M. GIALA
Thessaloniki, Greece

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ASPIRATION SYNDROMES IN PREGNANCY

Sir,—In the past decade it has become accepted practice to give oral alkali to patients in labour as prophylaxis against the acid aspiration syndrome.

We report two patients who received appropriate alkali therapy, in which the aspiration of alkaline stomach contents into the lungs during anaesthesia for Caesarean section resulted in differing clinical courses.

The first patient, a 25-year-old primigravida, underwent an emergency Caesarean section under general anaesthesia after prolonged labour. Routine precautions at induction did not prevent the regurgitation and inhalation of stomach content, which was seen as a clear yellow fluid. Tracheal intubation was performed rapidly, and a suction catheter was inserted via the tube. A healthy child was delivered by routine lower segment Caesarean section. After antagonism of residual neuromuscular blockade and removal of the tracheal tube, there was ventilatory inadequacy and peripheral circulatory collapse. The patient was transferred to the intensive therapy unit, for treatment of the acid aspiration syndrome. Investigations included chest radiography (fig. 1) and analysis of the gastric aspirate. The patient died 8 h after the induction of anaesthesia.

The second patient, a 32-year-old primigravida, underwent an emergency Caesarean section under general anaesthesia because of obstructed labour. Before induction a nasogastric tube was passed and the stomach aspirated. Following induction, tracheal intubation was carried out without incident. During the operation, the cuff of the tracheal tube burst, laryngoscopy was performed immediately, and the tracheal tube changed without incident. Ten minutes later the cuff of the second tube burst, and at laryngoscopy a pool of whitish, minty-smelling fluid was observed in the pharynx; this was removed by suction, and a third tracheal tube inserted. The operation was completed uneventfully, and the patient recovered fully from anaesthesia, but 30 min later she developed tachypnoea, cyanosis and tachycardia. Chest radiography (fig. 2) was performed, and the patient was transferred to the intensive therapy unit for treatment of the acid aspiration syndrome. The patient recovered completely.

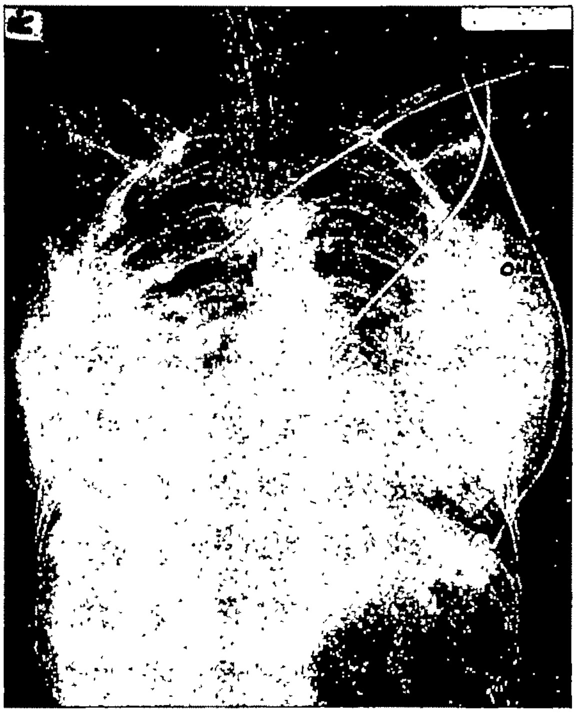

FIG. 1. Chest x-ray of first patient.

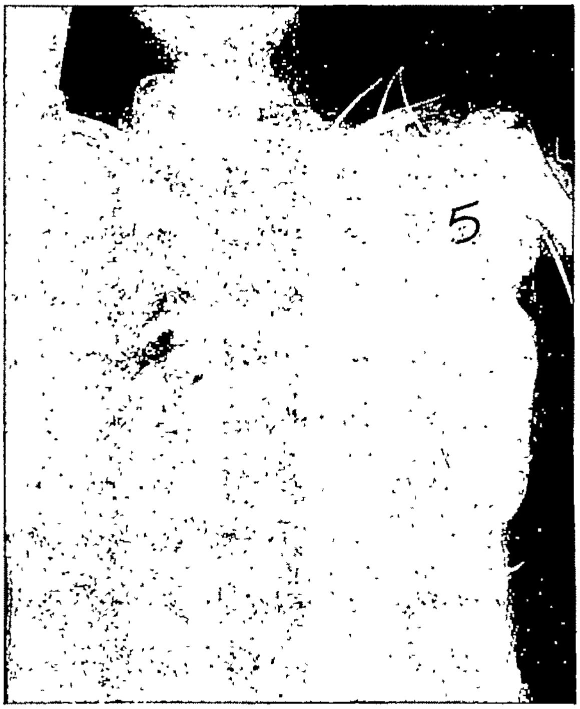

FIG. 2. Chest x-ray of second patient.

These two reports raise doubts about the efficacy of the magnesium trisilicate regime which has been so widely described in the U.K. and elsewhere (Crawford, 1972).

There is good evidence that an adequate regime, as recommended, had been carried out in these two patients. In the first patient, the documentation of individual doses of the drug was not complete, but a gastric sample obtained 90 min after the inhalation contained 14.3 mmol litre^{-1} of magnesium (four times the normal concentration) and with a pH 7.6 unit. In the second patient, seven doses of 15 ml of magnesium trisilicate BPC was recorded as having been administered during the course of a 10 h labour. In addition, the anaesthetist observed the colour and odour of the fluid pharyngeal contents at the time of the second tracheal incubation.

The chest x-ray appearances in these patients suggested massive inhalation by both patients, but the clinical course and blood-gas measurements were different, as was the outcome. These case reports pose three questions.

First, is it rational to add a volume of fluid to the stomach of a woman in labour in the knowledge that intestinal and gastric stasis (Nimmo, Wilson and Prescott, 1975) is a normal consequence of labour? In the first patient there was x-ray evidence of gastric dilatation.

Second, are the effects of the inhalation of magnesium trisilicate less dangerous than the aspiration of normal stomach contents? To a certain extent, the volume of gastric fluid may be controlled by diet, by the administration of apomorphine, or the passage of a wide-bore nasogastric tube.

An important factor which has been overlooked is that the administration of an antacid increases the rate of production of intragastric hydrogen ion six- to 20-fold (Price and Sanderson, 1956).

Third, does the administration of magnesium trisilicate induce a false sense of security on the part of the anaesthetist in relation to his technique? Does a properly conducted magnesium trisilicate regimen invariably produce an alkaline aspirate, or at least an aspirate with a pH in excess of 3.5?

The authors would suggest that it does not. In a series of 27 patients (table I), in whom the recommended regime had undoubtedly been administered, four of the patients had a gastric pH within the range described as being liable to produce the acid aspiration syndrome.

TABLE I. *Number of administrations of magnesium trisilicate B.P. 15 ml and analysis of gastric aspirate in 27 patients undergoing operative delivery*

	Mean	Range
Magnesium trisilicate doses	5.7	0.15
pH of gastric aspirate (unit)	6.6	1.5–9.0
Mg^{2+} concn in gastric aspirate (mmol litre^{-1})	87.1	0.6–370.0

G. A. H. Heaney
H. D. Jones
Sutton Coldfield

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BOOK REVIEWS

Monographs in Anaesthesiology, Volume 1,—Relief of Intractable Pain, 2nd edn. By Mark Swerdlow. Published by Elsevier/North Holland Biomedical Press, Amsterdam. Pp. 338; illustrated; indexed. Price $61.50.

Dr Mark Swerdlow is one of that pioneering group of British anaesthetists who, some 20 years ago, began the interest in intractable pain and in the establishment of pain relief clinics. This interest has grown rapidly, particularly in the past few years, to the extent that the subject of intractable pain has been referred to as "Medicine's new growth industry".

For this second edition of *Relief of Intractable Pain*, Dr Swerdlow has again collected 12 internationally recognized experts. Eight of them contributed to the first edition and there are four new contributors, one of whom, Professor Long—the leading expert in electrical stimulation—has written a new chapter on his subject so that there are now 11 chapters. Five of the authors work in the U.K., six in North America and one in Israel.

The first edition of this blook was published in 1974 and the advances in the subject since then can be seen by the frequent references in all the chapters to more recent work. The sequence of chapters now follows closely that proposed by a previous reviewer of the previous edition and this helps to give continuity. There is a pleasing uniformity of length and style in the chapters, making it easy to read.

The first chapter surveys the neurophysiological basis of pain perception, the emphasis being on the evidence from experimental and clinical observations in man. These are related to the diseases and conditions producing pain and to the methods of treatment. The importance of the periaqueductal grey matter, recently shown to be involved in the action of morphine, electrical stimulation and the encaphalins, is stressed. The writer, Amiram Carmon from Israel, has managed to make this complex subject easily understandable and has shown its relevance to clinical practice.

The second chapter on psychological aspects, by Merskey, covers the interrelationship between emotion and pain and the psychological methods of treatment, including hypnosis and biofeedback. The author believes that antidepressants may have an analgesic effect apart from their antidepressant action although, however, Bond has shown that they are only effective in cases of depression.

After a chapter on the management and function of pain centres by Bonica and Butler, which makes one envious of the facilities and man-power available in both treatment and research in the U.S., there are five chapters, practical and detailed, relating to treatment carried out in all pain relief clinics, even those with the minimum of facilities.

Foldes describes analgesics, hypnotics, antidepressants and the encephalins. Three chapters deal with injection therapy—peripheral nerve blocks (Churcher), intrathecal and extradural nerve blocks (Swerdlow) and sympathetic nerve blocks (Challenger). Each describes in detail (often accompanied by line diagrams, photographs and x-rays) techniques and indications. Both Swerdlow and Challenger mention in some depth the complications that can follow commonly used tecniques. It is unfortunate that, in the chapter by Swerdlow, no mention is made of the use of interathecal phenol for the distressing spasms which sometimes occur in patients with paraplegia, but Churcher does mention the use of paravertebral injections for this, although in practice the intrathecal route is easier. Long discusses the use of electrical stimulation in pain relief, ranging from stimulations applied to the skin, which are used for the relief of both chronic and postoperative pain, to devices which are implanted in various areas of the spinal cord and brain. He considers the mode of action to be related to conventional nerve physiology as modified by Melzack and Wall.

Apart from the mention that "brain stem–thalamic opiate receptor" may be concerned in the action of the stimulation and a personal communication from Melzack regarding the use of stimulation at trigger points or acupuncture points, no reference is made to the relation of electrical stimulation, encephalins and acupuncture. In fact, there is no reference to acupuncture at all in the book, although a number of reputable papers have been written on the subject in the past few years.

The last three chapters deal with techniques which are highly specialized and are carried out in relatively few pain relief clinics, although Lipton, who writes on percutaneous cervical cordotomy and pituitary injection, has popularized the former technique of which he is the acknowledged expert.

More sophisticated neurosurgical operations are described in the chapters by Watkins, and Jackson deals with the place of radiotherapy, anticancer drugs and hormone therapy in the relief of pain.

There are two appendices at the end of the 11 chapters. The first gives a useful table for the preparation of the agents used in injection therapy, the second is a survey of pain relief clinics throughout the world by the American Society of Anesthesiologists.

One can truly echo the plaudits which were accorded to the first edition of this book. The volume is essential for those who work in pain relief clinics and the growing number who are interested in the subject.

W. Sniper

The Isolated Heart–Lung Preparation. By P. H. Huisman and J. J. Schipperheyn. Published (paperback) by Martinus Nijhoff Medical Division. Pp. 41; illustrated; indexed. Price 25 guilders.

This pamphlet describes the production of a canine heart–lung preparation similar to that described by Starling, but modified by total denervation and the incorporation of a servo-controlled roller pump to provide right atrial filling and a linear capillary resistance to replace the Starling resistor. Electrolyte shift and cardio-metabolic changes occurring in the preparation over a period of hours are described together with factors which minimize the development of pulmonary oedema. The technique may be used for the study of haemodynamic changes in the lung and circulation and the study of factors affecting coronary blood flow and myocardial oxygen consumption.

Graham Smith

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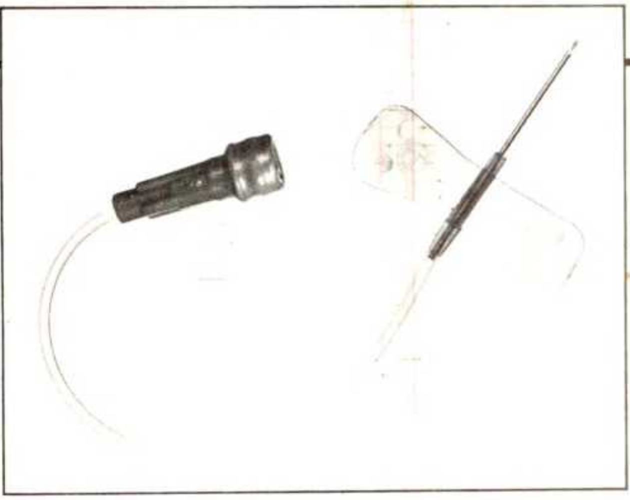

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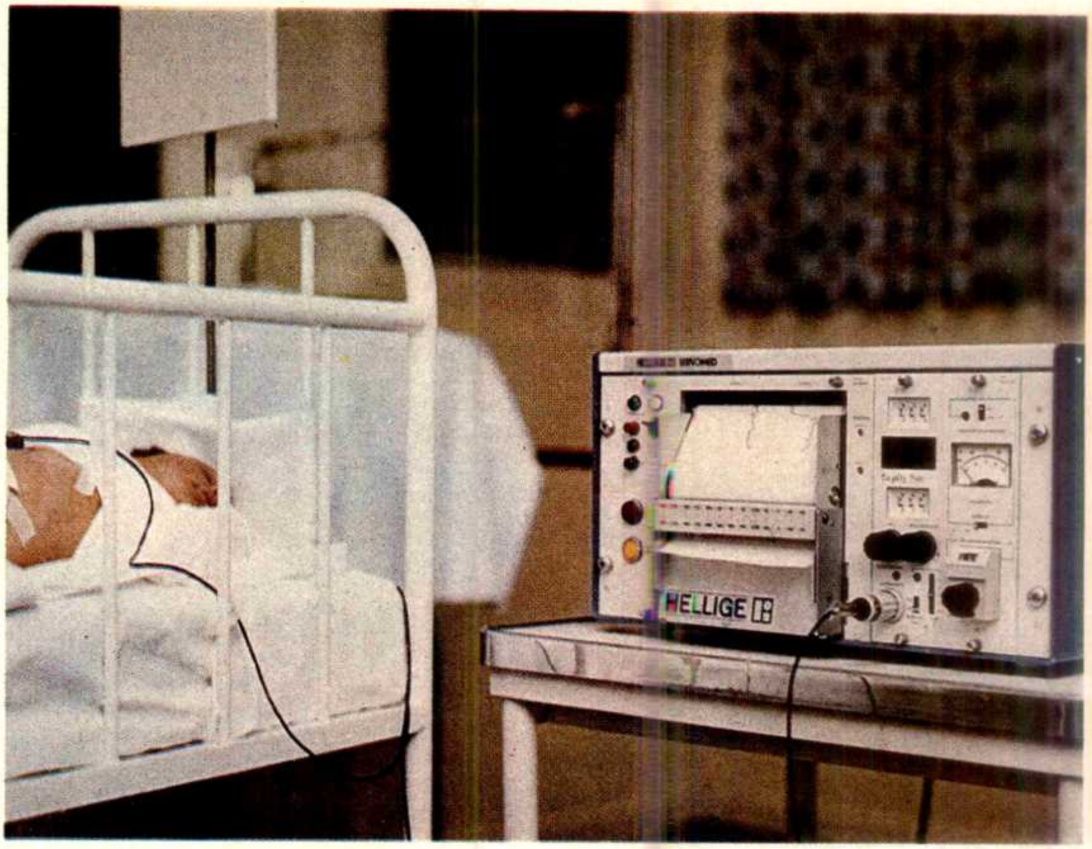

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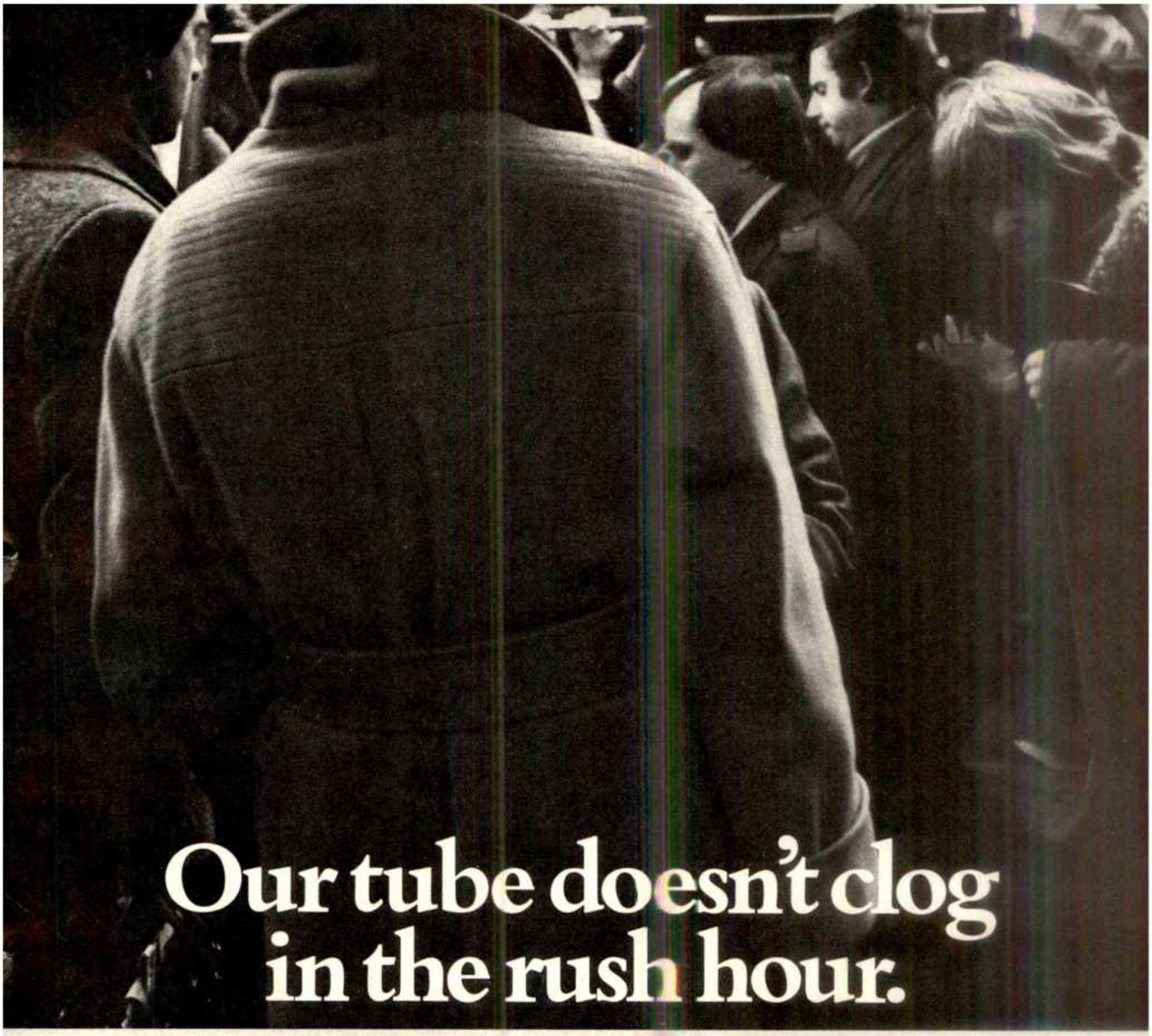
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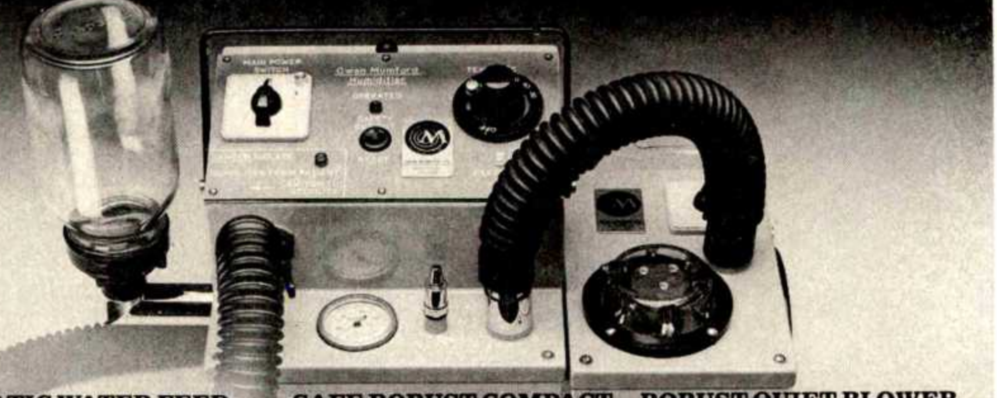

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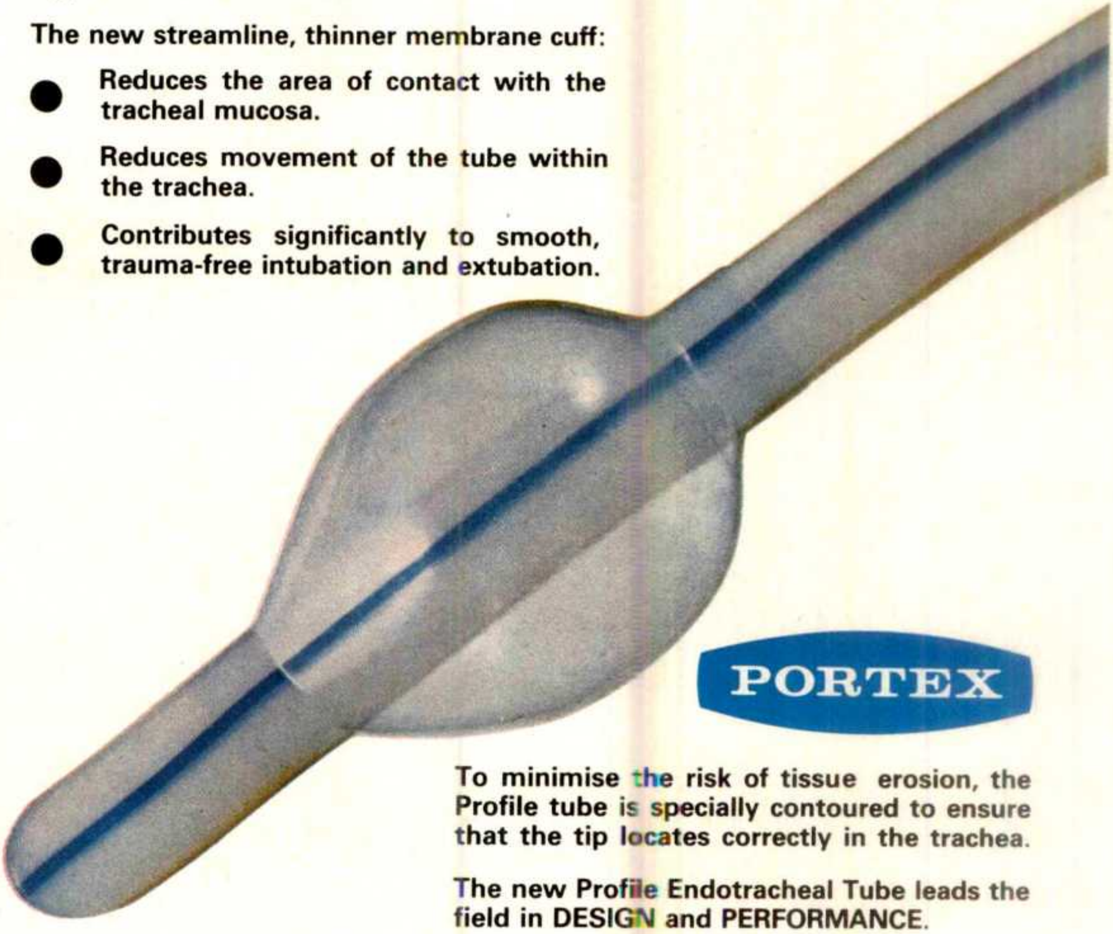

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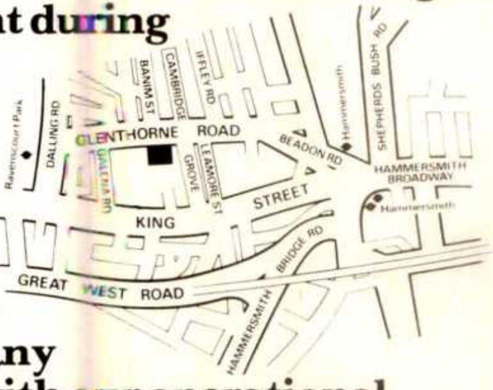

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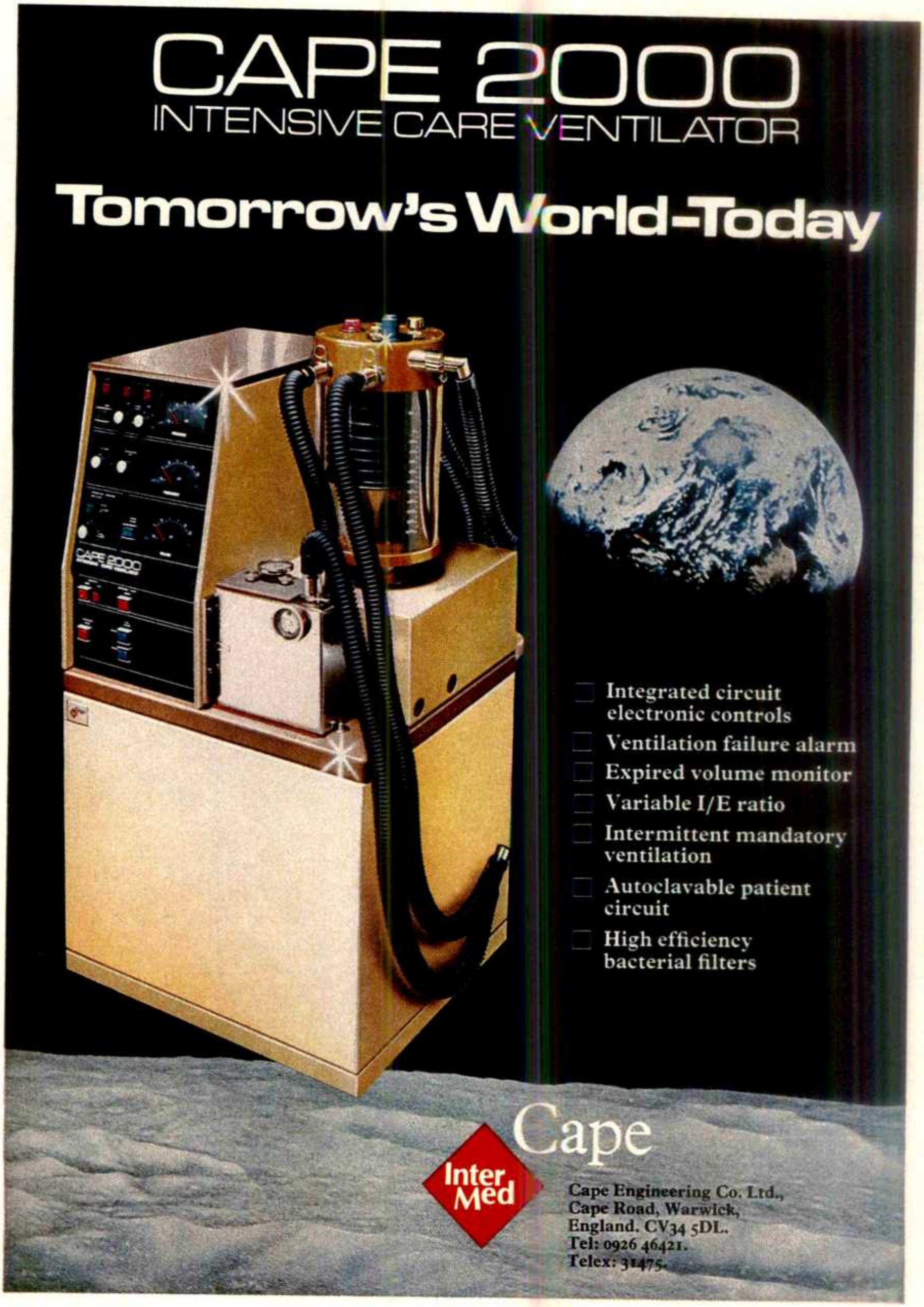

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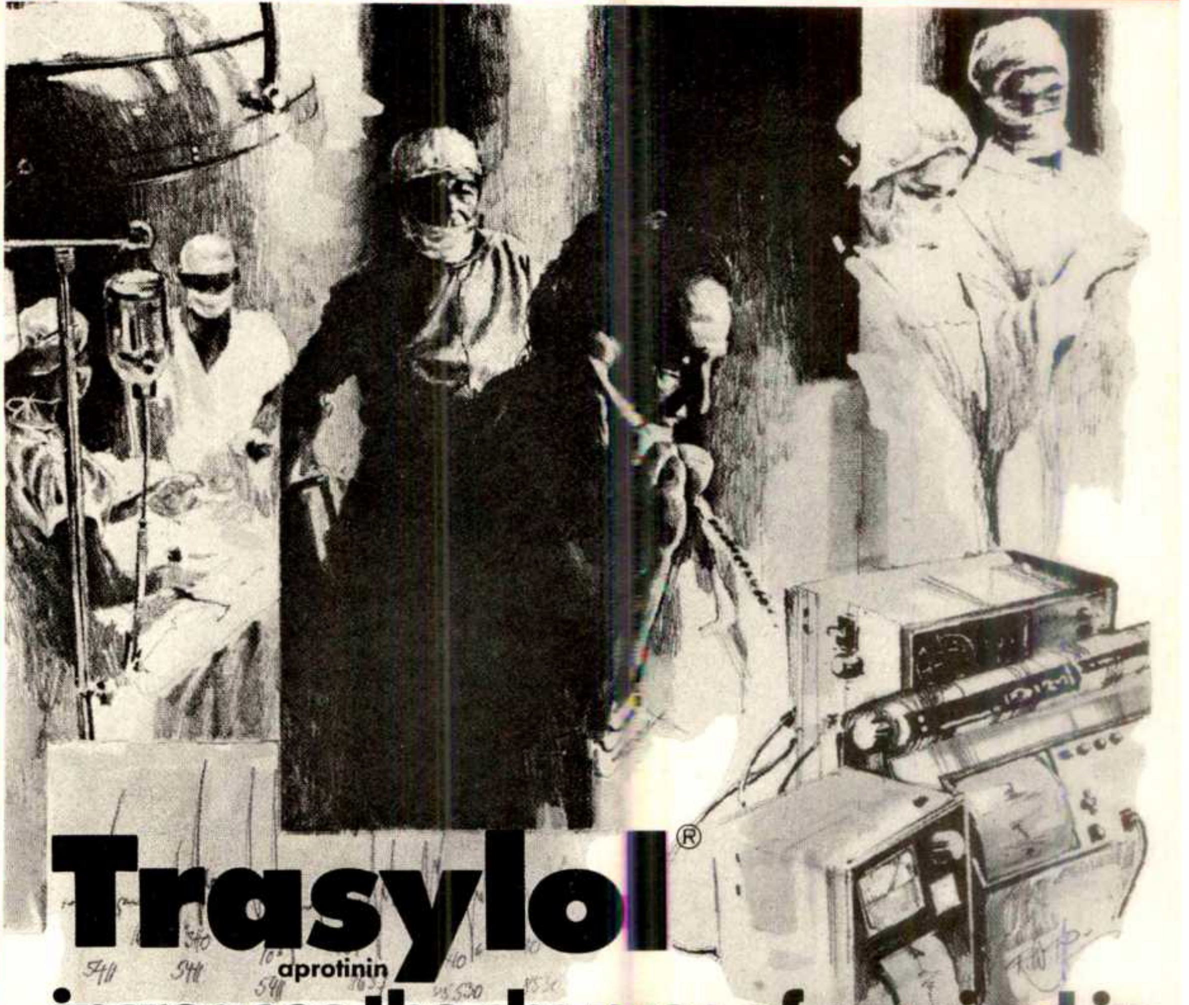

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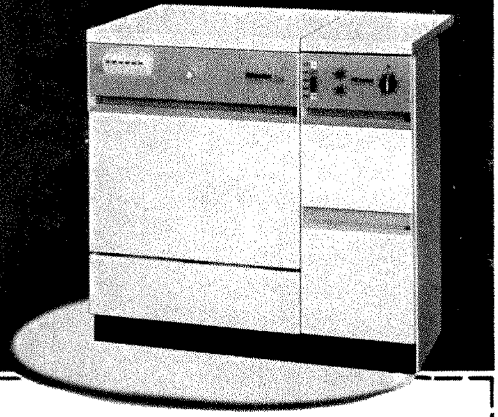

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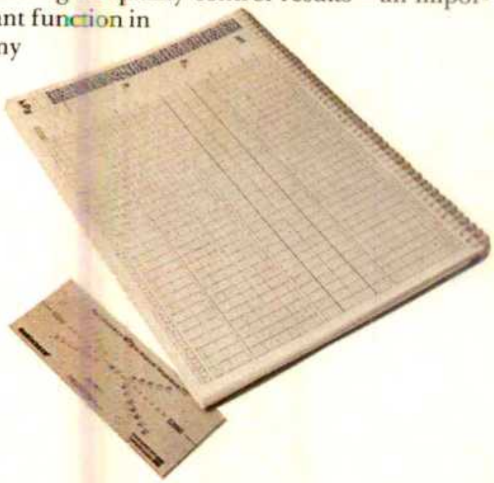

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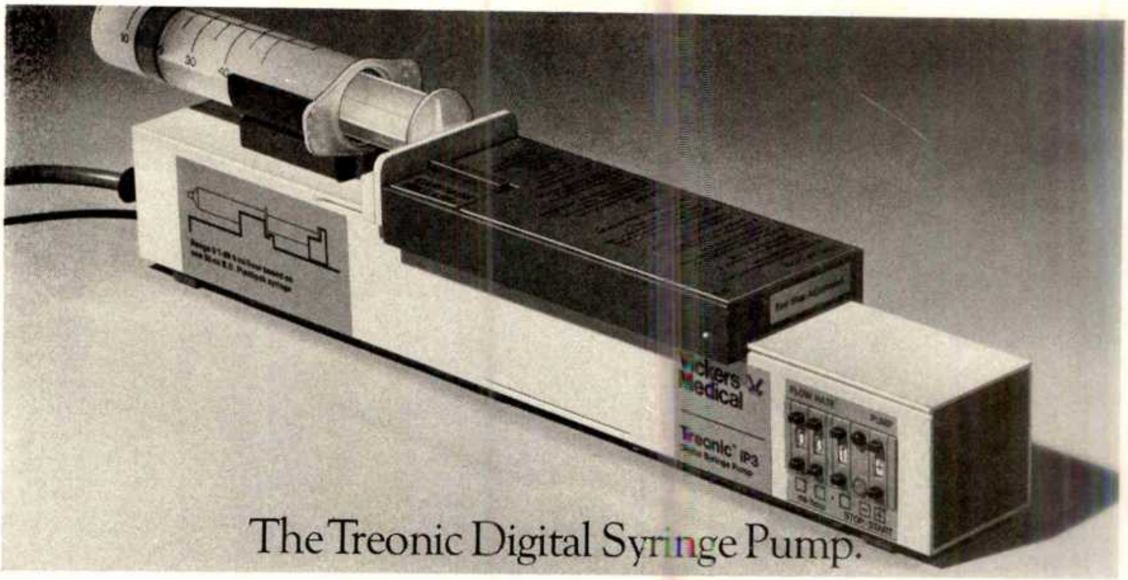

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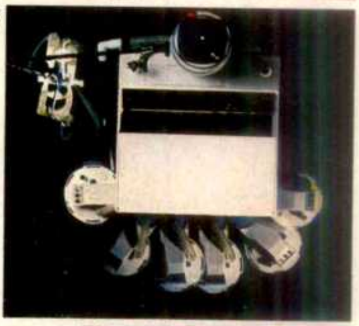

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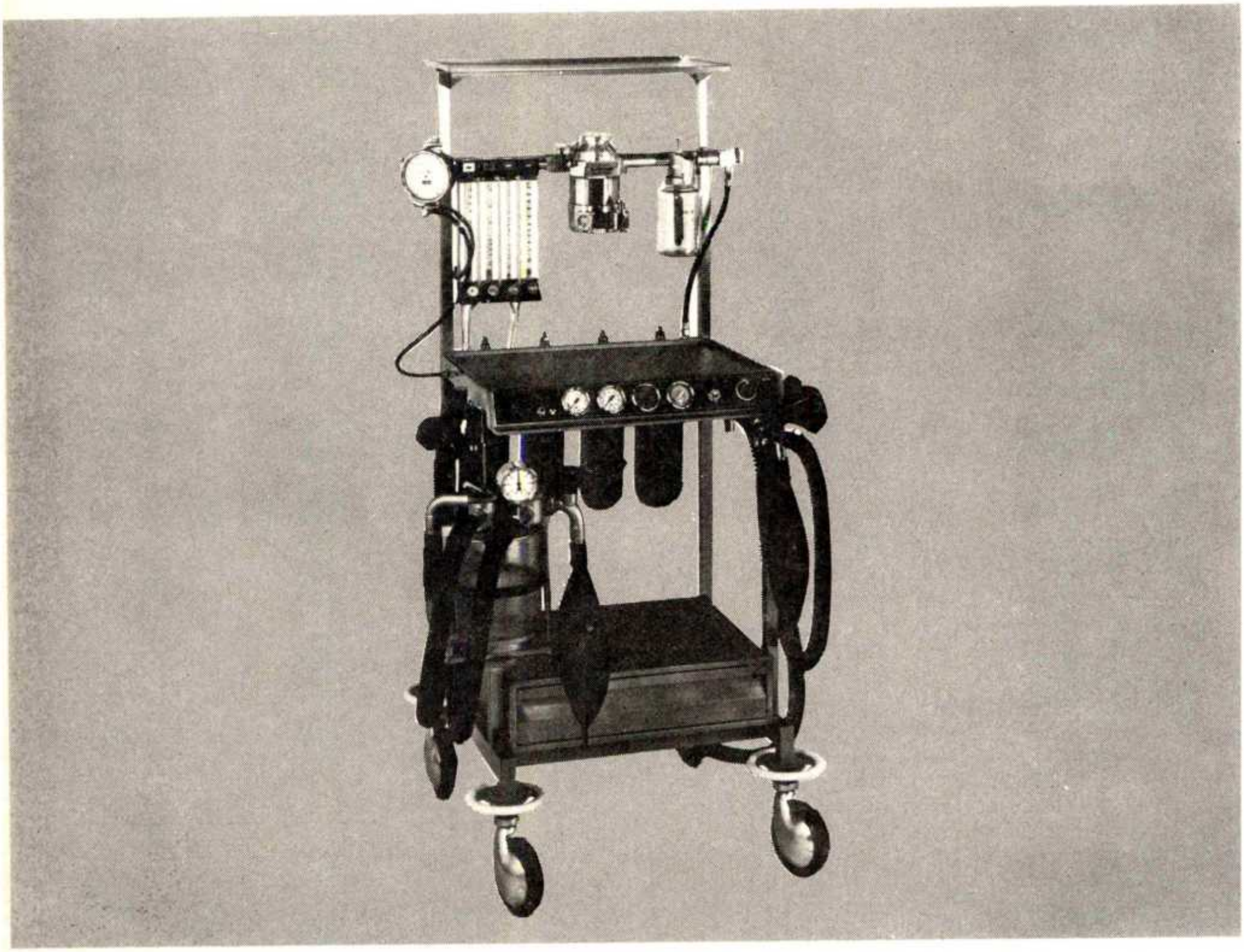

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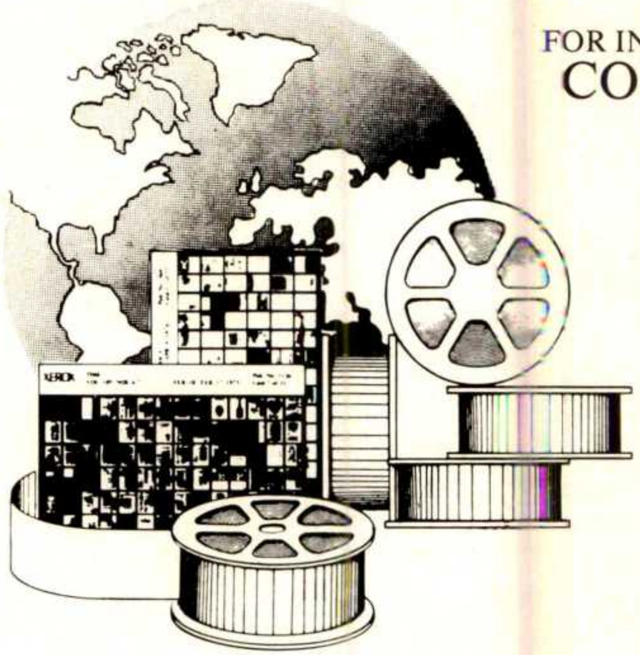

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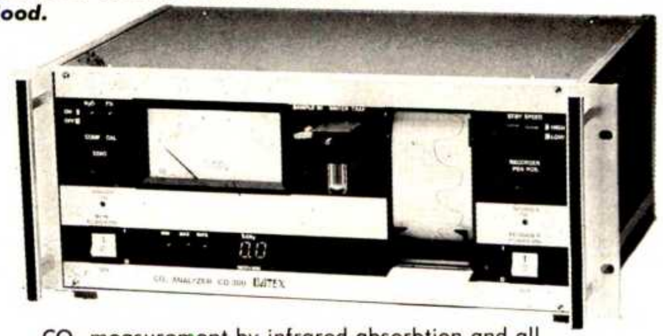

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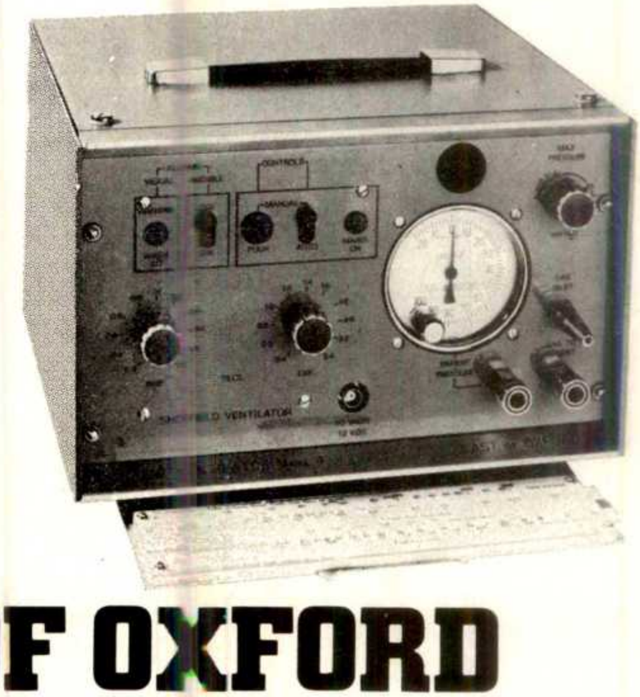

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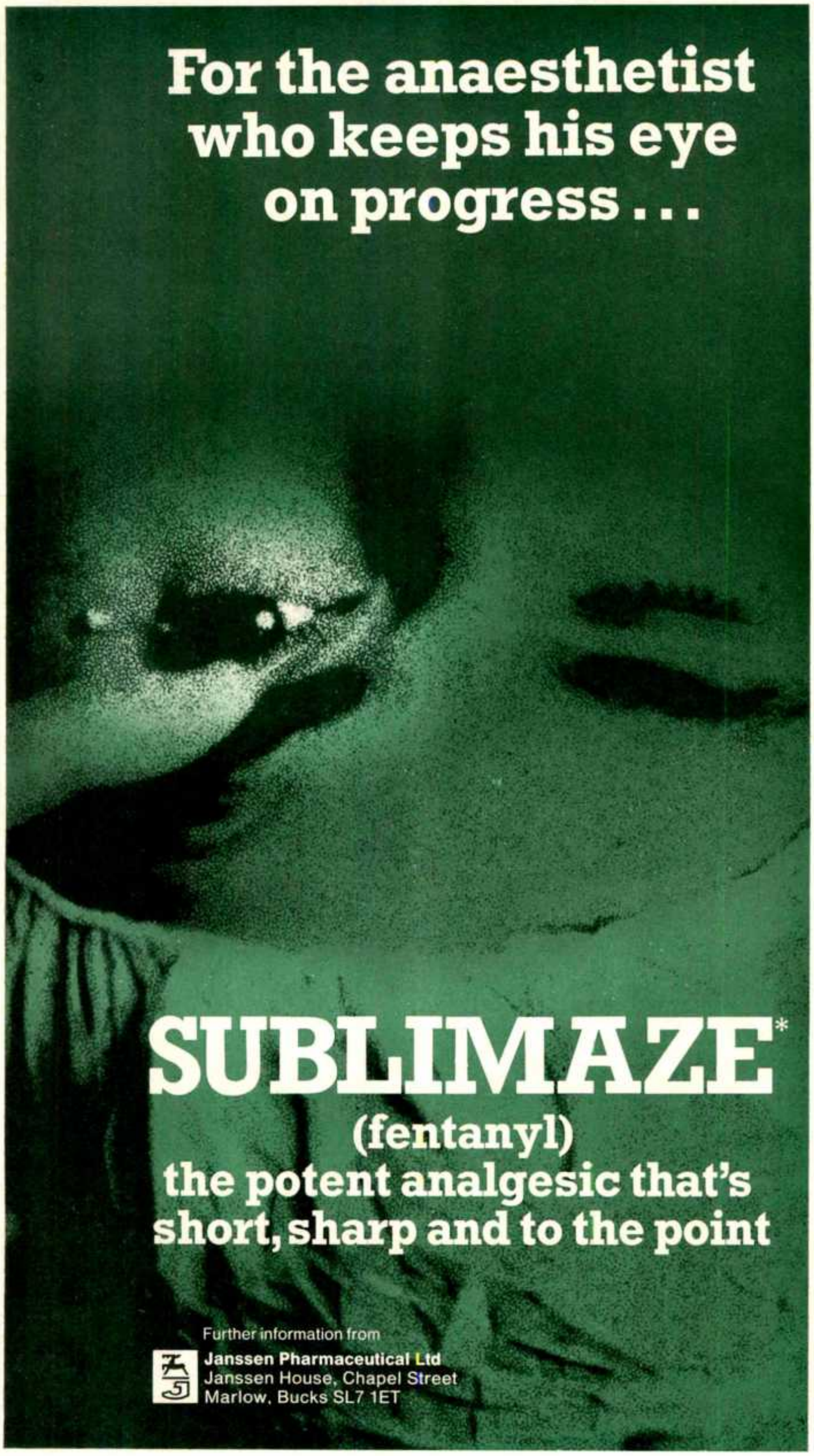
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BRITISH JOURNAL OF ANAESTHESIA

VOLUME 51 APRIL 1979

EDITORIAL

ANAESTHESIA OR CATALEPSIA FOR NEUROSURGERY?

The majority of anaesthetic drugs depress the central nervous system (c.n.s.), but some, for example ketamine and nitrous oxide, are capable of producing excitation and have been classified as cataleptoid c.n.s. stimulants (Winters, 1972). This cataleptic state is not strictly related to the condition described by clinical neurologists. Early pharmacological studies on ketamine by Corssen, Miyasaka and Domino (1968) suggested that the drug was both a stimulant and a depressant of the c.n.s., producing a state of dissociative anaesthesia. However, more recent studies of the effects of ketamine on the electroencephalogram (e.e.g.) (Kayama and Iwama, 1972; Wong and Jenkins, 1974) have shown that its overall effects are stimulant. Lack of awareness and analgesia may be secondary to cortical seizure activity in the same way that petit mal attacks are accompanied by loss of consciousness. In a study of cerebral blood flow (c.b.f.) in man, Hougaard, Hansen and Brodersen (1974) concluded that ketamine was probably not a direct cerebral vasodilator, but that the observed increase in c.b.f. was secondary to drug-induced changes in neuronal activity. Dawson, Michenfelder and Theye (1971) also demonstrated an increase in canine c.b.f. with ketamine and they were able to attenuate this response by the prior administration of thiopentone, a cerebral metabolic depressant drug (Pierce et al., 1962). Increases in intracranial pressure (i.c.p.) with ketamine have also been described in man by Shapiro, Wyte and Harris (1972).

Like ketamine, nitrous oxide is a potent cerebral vasodilator causing marked increases in i.c.p. in patients with intracranial disease (Henriksen and Jörgensen, 1973). Initially this was attributed to a direct action on cerebral vessels and this could be countered by hyperventilation, but recent observations suggest that it is secondary to neuronal stimulation (Misfeldt, Jörgensen and Rishöj, 1974; Phirman and Shapiro, 1977). An increase in i.c.p. produced by nitrous oxide in a patient was not modified when the arterial tension of carbon dioxide (Pa_{CO_2}) was reduced to 4.12 kPa, but the response was modified by the prior administration of sodium thiopentone.

Extreme hyperventilation, which may be used to prevent large increases in i.c.p. with nitrous oxide, may be harmful. Harp and Wollman (1973) described a study in man in which hyperventilation, for 1 h to Pa_{CO_2} 2.66 kPa, with nitrous oxide and oxygen produced an increase in cerebrospinal fluid (c.s.f.) lactate and a decrease in oxygen tension in the c.s.f. (c.s.f. $P\text{O}_2$). Hyperventilation to the same extent with halothane did not alter c.s.f. lactate or c.s.f. $P\text{O}_2$ and it was suggested that this was a result of improved perfusion secondary to the cerebral vasodilator action of halothane. An alternative explanation is that nitrous oxide causes cerebral metabolic stimulation which is normally accompanied by an increase in c.b.f., but this response is prevented by hyperventilation resulting in anaerobic metabolism.

The possible mechanisms of cerebral vasodilatation produced by halothane are of great interest, although these have not been fully elucidated and hypotheses advocated currently are conflicting. In very light halothane anaesthesia an increase in central bioelectrical activity has been reported (Mori and Winters, 1975) and this may account for the initial increase in c.b.f. Most studies have concluded that cerebral vasodilatation with halothane results from a direct action on the vessel wall (Smith and Wollman, 1972). Smith (1973) has reasoned that a decrease in cerebral metabolic rate for oxygen ($CMR\text{O}_2$) and autoregulation of cerebral venous oxygen tension may be responsible for this action, but a study by Albrecht and others (1977) concluded that halothane causes cerebral vasodilatation by a mechanism unrelated to $CMR\text{O}_2$. Recently Sakabe and others (1976) have demonstrated in man that during halothane in oxygen anaesthesia the addition of nitrous oxide caused a marked increase in c.b.f.

equivalent (blood flow in relation to the oxygen demand of the brain calculated as the reciprocal of the measured arterial–internal jugular venous oxygen content difference (Smith and Wollman, 1972)). Sakabe and others (1978) later showed in the dog that nitrous oxide increases both c.b.f. and $CMRo_2$ during halothane anaesthesia, and that this was not a result of sympatho–adrenal stimulation. McDowall, Harper and Jacobsen (1963) showed that halothane vaporized in air reduced c.b.f. in canine brain, but subsequently it was shown (McDowall and Harper, 1965) that halothane vaporized in nitrous oxide increased flow above the control; when air was administered in place of nitrous oxide c.b.f. decreased below the control value.

Is this cerebral vasodilator action of halothane related to cerebral metabolic stimulation? Most workers have held the view that nitrous oxide has minimal effects on $CMRo_2$ but Theye and Michenfelder (1968), like Sakabe and others (1978), demonstrated an increase in dogs. However, the e.e.g. during nitrous oxide administration may be synchronized at a fast frequency which may be indistinguishable from that of a conscious subject, relaxed with his eyes closed (McDowall, 1976). In addition, power spectrum analysis of the e.e.g. has shown that in patients anaesthetized with nitrous oxide supplemented with light halothane, methoxyflurane or narcotic analgesics, arousal patterns may appear, and these are frequently associated with cardiac arrhythmia, hypertensive responses or alterations in respiratory patterns when spontaneous ventilation has been retained (Stockard and Bickford, 1975; Bimar and Bellvile, 1977). These responses were not necessarily linked to any surgical manoeuvre.

There has been some concern about the use of enflurane in neuroanaesthesia because of its propensity to induce seizures which are associated with marked increases in c.b.f. and $CMRo_2$ (Michenfelder and Cucchiara, 1974). It has been demonstrated recently that seizure activity with enflurane is augmented by nitrous oxide (Smith et al., 1978).

Some recent studies on the effects of nitrous oxide on brain are difficult to interpret, but this may be related to species differences. One may speculate that its actions are biphasic, causing stimulation at light levels of "anaesthesia", but potentiating any existing cerebral metabolic depression. Carlsson and his colleagues (1976) showed that the administration of nitrous oxide to rats which were sedated or anaesthetized with diazepam resulted in decreases in both c.b.f. and $CMRo_2$. However, these workers could not demonstrate a decrease in $CMRo_2$ with diazepam alone, although Maekawa, Sakabe and Takeshita (1974) found that it reduced canine c.b.f. in parallel with $CMRo_2$. Similar reductions in response to diazepam have been described also in man following head injury (Cotev and Shalit, 1975). The work of Sakabe and colleagues (1978) is also difficult to interpret in that the e.e.g. was slowed while both c.b.f. and $CMRo_2$ increased following the administration of nitrous oxide during background halothane anaesthesia.

Most of the observations which have been discussed emphasize the need to avoid ketamine and to provide adequate supplementation of a nitrous oxide in oxygen technique in neuroanaesthesia. This may be particularly important when cerebral ischaemic hypoxia is present or induced, for example by the application of a temporary clamp on a main vessel feeding an intracranial aneurysm. Lightfoote, Molinari and Chase (1977) have shown that the type of anaesthetic (stimulant or depressant) can affect the size of an infarct in various animal stroke models. They found that cerebral infarction during ketamine anaesthesia substantially exceeded that occurring with barbiturates and they suggested that these studies should assist in the development of new pharmacological approaches to limiting ischaemic brain injury in man. Narcotic analgesic or light halothane supplementation of nitrous oxide may not be sufficient for this purpose but drugs such as barbiturates or Althesin can improve perfusion of ischaemic areas by reducing total c.b.f. and i.c.p. and their use has been recommended when there is a possibility of cerebral infarction (Hoff et al., 1974). There may also be a place for the use of halothane or enflurane vaporized with oxygen-enriched air and with a continuous Althesin i.v. infusion, a combination known to reduce cerebral activity (Dubois et al., 1978). Total i.v. anaesthesia with Althesin and fentanyl may be useful also for avoiding anaesthetic gas pollution and preventing nitrous oxide amplification of air during air encephalography. Finally, it should be emphasized that neurosurgery is performed most easily on a resting brain, particularly during cerebral vascular surgery or when brain compression is present.

John Barker

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THE EDITOR wishes to apologize for two errors which appeared in our February Editorial (*Br. J. Anaesth.*, 1979, **51**, 79).

The reference to Thorburn and Moir relates to a report in preparation (this was not published in 1978 as indicated). The editorial staff is well aware of the difference in spelling between the name of Dr Mendelson and that of the celebrated composer. We are grateful to the large number of readers who took the trouble to point out our shortcomings in this respect and hope that they will accept in mitigation the fact that the correct spelling appeared on the second last line of the Editorial.

Br. J. Anaesth. (1979), **51**, 273

CYTOTOXIC EFFECTS OF PROCAINE, LIGNOCAINE AND BUPIVACAINE

J. E. STURROCK AND J. F. NUNN

SUMMARY

Cytotoxic effects of procaine, lignocaine and bupivacaine were investigated on cultures of Chinese hamster lung fibroblasts. Cell growth was inhibited over 24 h exposures with an ED_{50} of 0.17% for procaine, 0.07% for lignocaine and 0.02% for bupivacaine. Cell survival (measured as colony-forming ability) was reduced over 24 h exposure with an ED_{50} of 0.21% for procaine, 0.09% for lignocaine and 0.06% for bupivacaine. Morphological changes included vacuolation, cell rounding and retraction from the surface on which the cells were growing. Motility was reduced to about 50% of control by lignocaine 0.1%. On removal of the local anaesthetics, cell growth was resumed after about 15 h without evidence of chromosome damage. Corresponding changes induced by inhalation anaesthetics are only seen at two to three times the minimal alveolar concentration required for anaesthesia.

De Jong (1977) has written of the remarkable lack of evidence for cytotoxicity of local anaesthetics when used in single doses, and this view is supported by a wealth of clinical experience. However, degenerative changes have been observed following repeated injections of bupivacaine to muscle (Sokoll, Sonesson and Thesleff, 1968; Libelius et al., 1970), and this raises doubts about the safety of repeated injections used, for example, in pain relief after operation. Prolonged exposure of cell cultures to local anaesthetic agents has shown clear evidence of toxic effects at concentrations which are generally well below those which are used in clinical practice.

Local anaesthetics cause a pronounced reduction in cell growth rate *in vitro* (Spångberg and Isaksson, 1970; Jackson, 1971; Jackson and Epstein, 1971; Gail and Boone, 1972). There is also clear evidence that they produce many types of cytotoxic side-effects; these include effects on the cell membranes, such as inhibition of cell fusion (Poste and Reeve, 1972) and effects on cell adhesion and spreading (Giddon and Lindhe, 1972; Rabinovitch and DeStephano, 1974, 1975; Nicholson, Smith and Poste, 1976). Also reported are effects on cytoskeletal elements, such as microtubules and microfilaments (Fink et al., 1972; Nicholson, Smith and Poste, 1976), the induction of vacuoles within the cell cytoplasm (Yang, Strasser and Pomerat, 1965) and inhibition of cell motility (Gail and Boone, 1972). There have also been reports of damage to muscle cells caused by single injections of various local anaesthetic agents (Benoit and Belt, 1970, 1972).

The objects of the present study were to compare the effects of lignocaine, procaine and bupivacaine on growth rate and on the viability of cultured cells, measured by colony-forming ability. By means of time-lapse cinephotomicrography we were able to observe the time course of the effects of lignocaine on the division rate and morphology of these cells.

METHODS

Growth rate and colony-forming ability

Chinese hamster lung fibroblasts were grown in Eagle's medium, as described previously (Sturrock and Nunn, 1975). Approximately 4–6 × 10^5 cells were seeded into 90-mm plastic Petri dishes and left to attach and increase overnight. Lignocaine or procaine was dissolved in distilled water, the pH of the solution being adjusted to 7.2 if necessary, and the solution filtered for sterilization. Suitable dilutions were made with saline and the required volumes were added to the medium in the dishes. Bupivacaine, being poorly soluble, was dissolved in a large volume of Eagle's medium and filtered; the dishes were then emptied, without disturbing the cells, and refilled with the drug medium in suitable dilutions.

Cells were exposed to local anaesthetic drugs in the medium covering them for 3, 24 and in some cases 48 h. After this time the medium was discarded, the dish was washed with saline and the cells were removed from the plastic surface with trypsin 0.25%.

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After 10 min fresh medium was added to inactivate the trypsin and dilute the cells to convenient numbers. The cell suspension was passed through a hypodermic needle to separate the cells, which were counted in a haemocytometer. They were then diluted with fresh medium and seeded into 50-mm plastic Petri dishes in order to grow into colonies for the calculation of colony-forming ability (CFA) as described previously (Sturrock, 1975).

Extra dishes with an inoculum similar to that of the treated dishes were trypsinized and counted at the start of each experiment; these were used with the final growth figures to calculate the growth rate. Controls were also set up without local anaesthetic agents. It was not possible to obtain repeatable results for growth rate during 3-h exposures, as during local anaesthetic treatment there was very little cell increase during the first few hours.

Morphology

Photomicrographs on 35-mm film were taken of living and of fixed and stained cells, using phase-contrast objectives ×40 or ×100. These photographs were made from cells exposed to lignocaine 0.2% or to procaine 0.1, 0.2 or 0.5%, for a duration of 24 or 48 h. The cells were growing on glass slides lying in Petri dishes and covered with medium containing the anaesthetic.

Time-lapse phase-contrast cinephotomicrography was undertaken, as described by Sturrock and Nunn (1975), except that the cells were growing in a 40-ml tissue culture plastic bottle for these experiments. A low flow of humidified air with 5% carbon dioxide was passed into the bottle. At the end of a control film of untreated cells for 20 h, the bottle was removed from the stage and the medium replaced with medium containing 0.1% lignocaine HCl. Filming continued on a new field of cells, as it was technically impossible to return to the original field. After a 24-h exposure to lignocaine 0.1% the bottle was again removed, the drug medium was discarded and the cells were washed twice with fresh medium. Five millilitre of fresh medium was then added to the bottle, which was replaced and a new field was filmed to record the recovery period. The microscope objective used was ×10 phase and there was one exposure every 2 min. The resulting film was later examined with a Spectro analysing projector. Numbers of mitoses were counted, in 4-h periods, during the three stages of the film and the appearance of the cells at the end of each 4-h period was noted. The cells were described as rounded-up for division, spread out on the plastic surface, or in an intermediate partly rounded state.

Persistence of local anaesthetic in culture

There was a possibility that the local anaesthetic agents were biotransformed by the cells and this would limit the effective duration of exposure to less than the exposure times which were planned. Therefore medium containing local anaesthetic drug was decanted after prolonged exposure to cells and was found to be indistinguishable in its effects from the same quantity of the local anaesthetic recently added to the medium. It was concluded that biotransformation of the local anaesthetic agents was not an appreciable factor in these studies.

RESULTS

Growth rate

Growth rate in cells exposed to each of the three local anaesthetic agents was depressed in relation to the concentration of the drug (fig. 1). The effect was slightly greater when the duration of treatment was increased from 24 to 48 h. Comparing the figures for ED_{50}, lignocaine was more than twice as effective, and bupivacaine about eight times as effective as procaine (table I). The regression line for 24 h of

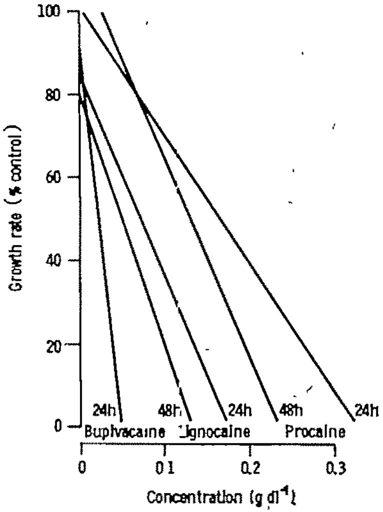

FIG. 1. Growth rate of Chinese hamster (CH) cells (expressed as a percentage of control) plotted against concentrations of three different local anaesthetic agents for 24- or 48-h exposures. Calculated regression lines are shown and values for n and r are in table I. All correlation coefficients are highly significant ($P < 0.001$).

TABLE I. *Effect of three local anaesthetic agents on growth rate of CH cells*

Local anaesthetic	Duration of exposure (h)	ED_{50}% i.e. (g dl^{-1})	*n*	*r*
Procaine	24	0.17	9	−0.98
	48	0.13	5	−0.98
Lignocaine	24	0.07	15	−0.94
	48	0.05	11	−0.88
Bupivacaine	24	0.02	5	−0.96

exposure to bupivacaine is particularly steep and because of the toxicity of this anaesthetic to the cells, no observations were made after 48 h exposure.

Cell survival (measured as CFA)

Cell survival was also impaired as a linear function of the concentration of the anaesthetics (figs 2, 3).

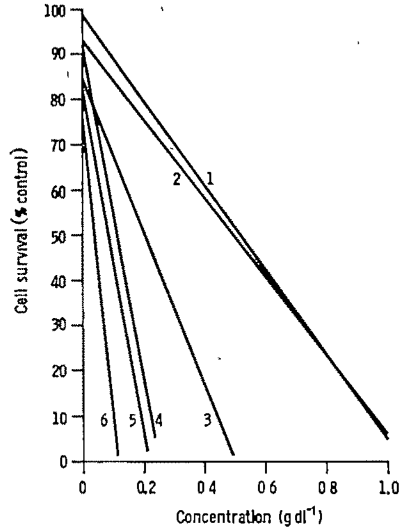

FIG. 2. Cell survival of CH cells (expressed as a percentage of control) plotted against concentrations of procaine and lignocaine for 3-, 24- and 48-h exposures. Calculated regression lines are shown and values for *n* and *r* are in table II. All correlation coefficients are highly significant ($P < 0.001$). 1 = procaine, 3 h; 2 = lignocaine, 3 h; 3 = procaine, 24 h; 4 = procaine, 48 h; 5 = lignocaine, 24 h; 6 = lignocaine, 48 h.

Three-hour exposures had similar effects in the case of procaine and lignocaine, with ED_{50} values of 0.5%. The effect was much greater after 24 and 48 h exposures, after which lignocaine was more than twice as toxic as procaine. Bupivacaine (fig. 3) was effective after 3 h, with an ED_{50} of only 0.1%. Although increasing the duration of exposure had a very pronounced effect on the action of lignocaine and procaine, it had relatively less effect in the case of bupivacaine.

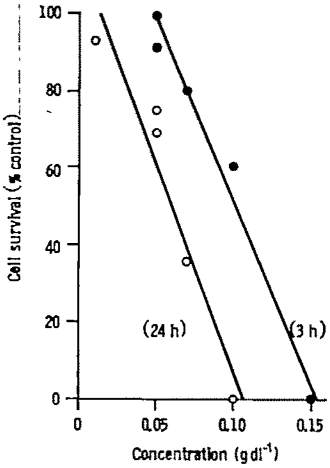

FIG. 3. Cell survival of CH cells (expressed as a percentage of control) plotted against concentrations of bupivacaine for 3- and 24-h exposures. Calculated regression lines are shown: values for *n* and *r* are in table II. Both correlation coefficients are highly significant ($P < 0.001$).

Mitosis

Cell numbers increased steadily during the 20 h of the control part of the film but, during exposure to lignocaine (0.1%), there was only one mitosis in 24 h and no increase in cell numbers (figs 4, 5). In the recovery period there was one mitosis in the first 4 h, but from 12 h onwards cell numbers and mitoses increased at normal growth rate until 36 h. After this

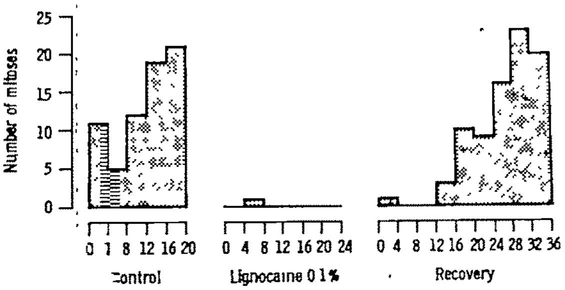

FIG. 4. Frequency of mitoses observed in cine film. Control period of 20 h, followed by exposure to lignocaine 0.1% for 24 h, then recovery during 36 h, after removal of anaesthetic.

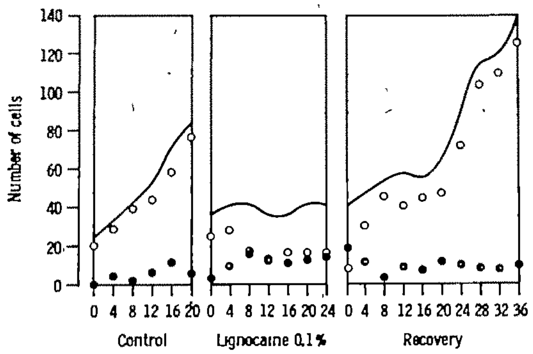

FIG. 5. Morphology of cells as seen in cine film (see fig. 7) in three different fields. —— = total cells; ○ = spread cells; ● = rounded cells. A number of intermediate types were only included in the totals. Abscissa shows time in hours.

time growth rate decreased as the surface of the bottle became overcrowded.

Morphology

The major changes seen were vacuolation, cell rounding and retraction from the surface on which they were growing (figs 6, 7). At the greater concentrations, cells rounded up and many became detached from the dishes, but on examination only a proportion of these were dead, the remainder being capable of reattachment and entering division. For this reason, when the contents of a high-dose dish were trypsinized and counted, it was necessary to centrifuge the overlying medium, to recover floating cells.

Cells in the film showed the first appearance of vacuolation within 1 h of contact with 0.1% lignocaine (fig. 7). Thereafter the vacuoles increased steadily in size and numbers, and the film also showed the progressive disappearance of spread cells (fig. 7). Cells rounded up as if for division, but no mitosis occurred and eventually they spread out again. There were also many cells which were contracted, but not circular in shape and in figure 5, these "intermediate" cells were included only in the total counts. During the period of exposure to lignocaine 0.1% cell motility as seen in the film was significantly reduced from a mean distance travelled of 73 μm per 3.3 h ($n = 11$, SEM = 12.7) to a mean distance of 35 μm per 3.3 h ($n = 13$, SEM = 11.6). Exposure to procaine 0.1% for 24 h resulted in more and larger vacuoles than with lignocaine 0.1% (fig. 6). Cells observed after exposure to bupivacaine 0.05–0.1% for 24 h appeared shrunken and contained small vacuoles.

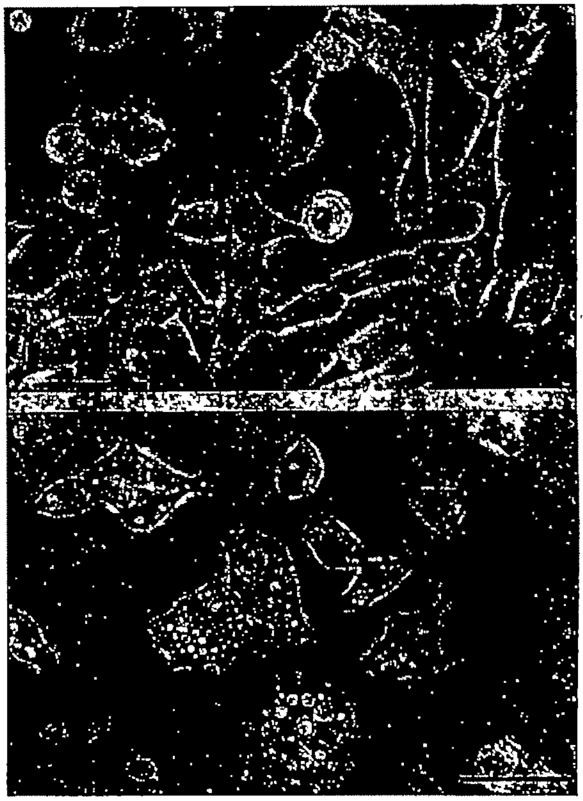

FIG. 6. Typical appearance of CH cells, (A) under control conditions and (B) after 24 h exposure to procaine 0.1%. The field was chosen to show mainly spread cells in which the vacuoles were most easily seen. Black lines represent 50 μm.

Recovery from 24 h exposure to lignocaine (0.1%)

During this phase cell motility returned to normal, but vacuoles were still present in some cells until more than 6 h after the medium change. Two cell deaths were observed between 15 and 16 h after the start of the recovery period, although, at that time, morphology had generally returned to normal appearances and cell division had resumed.

DISCUSSION

Growth rate

Our results for the effect of lignocaine on CH cells are in good agreement with those of Jackson and Epstein (1971) and Jackson (1971) for rat hepatoma cells. The mouse fibroblasts exposed to procaine by Gail and Boone (1972) seem to have been more sensitive than our cells as they reported no cell increase with only 0.07% procaine. Spångberg and Isaksson (1970) had results similar to ours when they

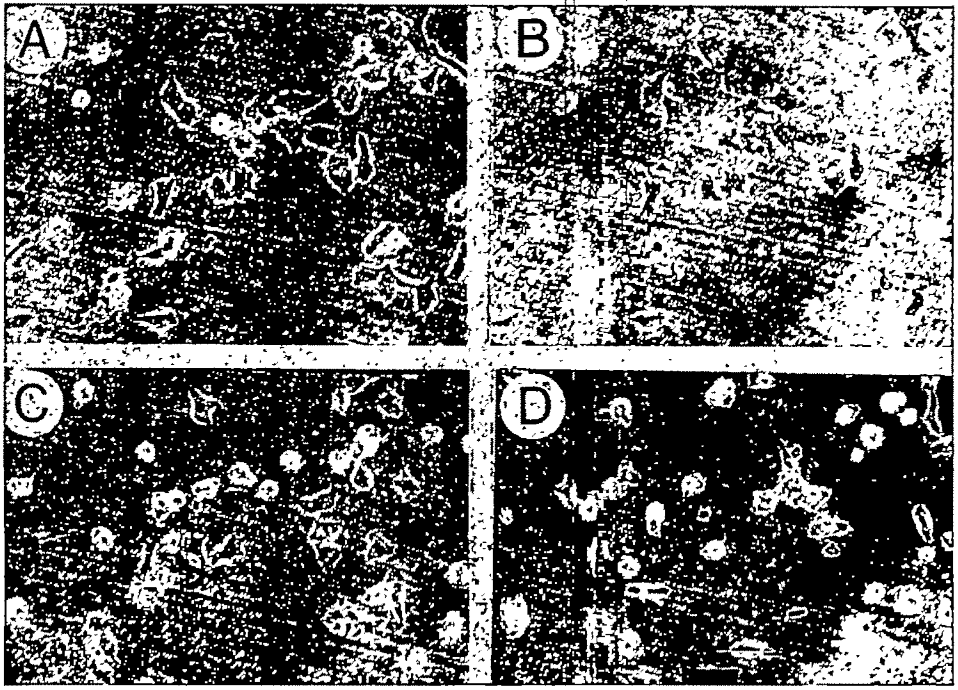

FIG. 7. Stills from the cinephotomicrography (fig. 5). A = commencement of exposure to 0.1% lignocaine; B = after 1 h of exposure; C = after 5½ h of exposure; D = after 18 h of exposure. The black line represents 50 µm.

exposed HeLa cells or human fetal skin fibroblasts to bupivacaine.

Thus it seems that cells from three different much-used lines of rodent cells, one old-established human tumour cell line and one fetal human cell were all very sensitive to suppression of mitosis by the various local anaesthetic agents tested *in vitro*.

There seems to be little doubt that local anaesthetic drugs are far more toxic to cell growth than are general anaesthetic agents. ED_{50} values reported in table I are all of the order of one-tenth of the concentrations in clinical use. This may be contrasted with ED_{50} values for the effects of general anaesthetic agents on growth of the same cell line which were, in general, two to three times the minimal alveolar concentration required for anaesthesia (Sturrock and Nunn, 1975).

Comparison of ED_{50} values with concentrations producing equivalent nerve blockade is difficult because relative potencies of local anaesthetics are not well established and relative Cm values (de Jong, 1977) do not seem to accord well with clinical experience. On the basis that lignocaine is twice as potent as procaine and bupivacaine is eight times as potent as procaine (Covino and Vassallo, 1976), the ratio between the ED_{50} and the concentrations used in clinical practice is much the same for all the three local anaesthetic agents which were studied.

It will be noted from figure 4 that recovery of cell division was considerably delayed when the local anaesthetic was withdrawn. This may be contrasted with the rapid commencement of DNA synthesis following withdrawal of halothane, which had prevented the onset of the DNA synthetic phase in synchronized cell cultures (Sturrock and Nunn, 1976).

Effect on the chromosomes

Cells exposed to concentrations of local anaesthetic agents that allowed some increase in numbers were seen to attempt mitosis, but metaphase was often protracted and ended with the cell spreading out again. In stained preparations (after hypotonic treatment) the chromosomes at metaphase were found to be scattered in the cytoplasm in a form similar to C-mitosis. This suggested that the microtubules of the mitotic spindle had been disrupted, preventing progression to anaphase. Cell cultures that were examined in the recovery period after removal of the local anaesthetic agent were seen to include many bi-nucleate and multi-nucleate cells, but no damage to chromosomes or polyploidy was seen. It is unlikely therefore, that local anaesthetic agents have any mutagenic effect as a result of chromosome damage.

Cell survival

The appearance of a cell, either under phase-contrast illumination or after fixing and staining, does not necessarily give any indication that it has lost the capacity for survival. Viable cells of the type we have studied invariably proceed to division; therefore loss of colony-forming ability (CFA) is a valid indication of loss of the capacity to survive.

The data in figures 2 and 3 and table II indicate a serious effect on cell survival with ED_{50} values much less than the concentrations which are clinically useful. In this respect, for 24 h exposures, procaine and lignocaine show toxicity almost in proportion to their potency, but bupivacaine is relatively less toxic. ED_{50} for reduction of CFA are of the order of one-tenth of the clinically useful concentrations of the local anaesthetic agents. This can be contrasted with the inhalation anaesthetic drugs for which ED_{50} for reduction of CFA is of the order of three to five times the minimal alveolar concentrations required for anaesthesia, except in the case of trichloroethylene (Sturrock, 1975).

TABLE II. *Effect of three local anaesthetic agents on viability of CH cells*

Local anaesthetic	Duration of exposure (h)	ED_{50}% i.e. (g dl^{-1})	*n*	*r*
Procaine	3	0.52	10	−0.92
	24	0.21	9	−0.90
	48	0.12	5	−0.82
Lignocaine	3	0.5	14	−0.89
	24	0.09	13	−0.90
	48	0.04	10	−0.94
Bupivacaine	3	0.1	5	−0.99
	24	0.06	5	−0.96

Morphological changes

The present study has confirmed the formation of vacuoles previously reported by Yang, Strasser and Pomerat (1965). Although the appearances such as those in figure 6B are bizarre, their significance is unknown. The disappearance of the vacuolated cells shown in figure 7 seems to result from a progressive increase in the number of cells which round up and thereby conceal their internal structure. Rounded cells are not seen in figure 6B because the field was selected to show a maximum number of spread-out cells with vacuoles. It is clear that vacuolated cells can recover when the local anaesthetic drug is withdrawn, and then proceed to division.

Other effects of local anaesthetic agents

Local anaesthetics also cause various metabolic effects in cultured cells, such as depression of oxygen uptake (Fink, Kenny and Simpson, 1968; Spångberg and Isaksson, 1970) and inhibition of synthesis of DNA, RNA and protein (Jackson, 1971), reduction in phagocytosis and metabolism in leucocytes and inhibition of PHA-stimulated lymphocyte transformation (Cullen, Chretien and Leventhal, 1972; Cullen and Haschke, 1974).

Overall cytotoxicity of local anaesthetic agents

There is now overwhelming evidence that local anaesthetic drugs produce major toxic effects on several cell functions, including cell division and survival. It is perhaps especially significant that these effects are exerted at concentrations well below those which are used for nerve blocks and infiltration anaesthesia. In contrast, the inhalation anaesthetics exert comparable effects only at concentrations which are substantially greater than those attained during normal anaesthesia.

It is by no means clear how these facts accord with the remarkable clinical safety of the local anaesthetic drugs. For example, continuous sciatic nerve block with very high concentrations of lignocaine, maintained for as long as a week, was followed by a rapid return to normal nerve conduction when the lignocaine was withdrawn (Robert and Oester, 1970; Bisby, 1975). Admittedly, cell division plays no part in axonal conduction and it would seem that neurones are more resistant to the cytotoxic effects of local anaesthetic agents than are the modified fibroblasts observed in the present study. Nevertheless, it would be reasonable to expect considerable damage to surrounding tissues, as has been reported following repeated injections of bupivacaine into muscles (Sokoll, Sonesson and Thesleff, 1968; Libelius et al., 1970).

An important safety factor would appear to be the rate at which local anaesthetics are removed from the site of injection, but this does not appear to have been clearly established. Ballard (1968) investigated the disappearance of lignocaine from a subcutaneous site using an implanted cell fixed to moist subcutaneous tissue. His results indicated that subcutaneous injections of lignocaine had decreased to 50% of their initial concentrations after about 100 min. This would be generally compatible with the peak blood concentrations obtained after 15 min, which suggests that approximately 10% of a subcutaneous injection has entered the circulation by that time (Scott et al., 1972). If the half-life of an injected depot is about 100 min, then it follows that cytotoxic concentrations would be maintained for at least 3 h after an injection of 2% lignocaine, even without the addition of adrenaline. Tucker and Mather (1975) have studied the clearance of local anaesthetic drugs from the extradural space and report biphasic clearance of lignocaine with a half-time of about 20 min for lignocaine without adrenaline and 60 min for lignocaine with adrenaline. Twenty per cent of the injected dose remained after 4 h, with or without adrenaline.

In contrast with these observations, Åberg, Friberger and Sydnes, (1978) have recently reported that intradermal injections of tritiated mepivacaine had decayed to 25% of their initial injected radioactivity at only 10 min after injection and to less than 10% after 30 min. These results suggest rapid clearance of the injected depot and this need not be incompatible with the observed duration of anaesthesia, since the local anaesthetic may remain bound to its receptor site in the neuronal membrane after the extracellular pool has been removed. With two such conflicting studies, it would appear that there is scope for further research into the rate of decay of extravascular depots of local anaesthetic agents.

There is very little information on the effect of local anaesthetic drugs on wound healing, particularly with multiple injections. Morris and Tracey (1977), who had gained the clinical impression that local anaesthetic agents impair wound healing, undertook a study of the effect of a single injection of lignocaine on wound healing in the rat. They found that the tensile strength of the skin wound was reduced at 5 and 7 days in a dose-related manner, and at each concentration of lignocaine the effect was slightly enhanced by adrenaline. The results of an earlier study by Nilsson and Wendeberg (1957) are not directly comparable, but suggest that a single injection of lignocaine 1% with adrenaline (1 : 200,000) reduces the tensile strength of wounds in comparison with saline. Bodvall and Rais (1962) also studied the effect of single injections of local anaesthetic on wound healing and found that, in the case of traumatized tissue, there was a marked reduction in the proportion of wounds healing by first intention, with frequent occurrence of dehiscence. The effect was worse when a vasoconstrictor was added. In non-traumatized tissue, tensile strength of the wounds was reduced only when a vasoconstrictor was added to the local anaesthetic. These studies suggest that wound healing might be markedly impaired by repeated instillation of local anaesthetic agents into an abdominal wound for control of pain after operation.

Gerwig, Thompson and Blades (1951) successfully controlled pain after cholecystectomy by instillation of 2% procaine 3 ml, every 3 h, through polythene tubes placed beneath the anterior rectus sheath in the abdominal wound. They reported "no interference with tissue repair". Lewis and Thompson (1953) undertook a similar study with instillation of procaine into the rectus sheath and found "no delay in healing or any evidence of wound infection".

The histotoxicity reported in this study, together with the unequivocal evidence of impaired healing following a single injection of lignocaine in the study of Morris and Tracey (1977) suggests that there is a *prima facie* case that repeated instillation of local anaesthetic agents into surgical wounds might cause interference with wound healing. Similar considerations might apply to prolongation of the action of local anaesthetics by admixture with dextran (Loder, 1960, 1962).

Local anaesthetic drugs are also administered by continuous i.v. injection to control cardiac arrhythmia. The maximum dose does not usually exceed 3 mg min^{-1} of lignocaine and the rate of biotransformation should be sufficient to prevent cytotoxic concentrations accumulating in the body and, indeed, toxic effects on the cardiovascular and central nervous systems will probably limit dosage before cytotoxic concentrations are reached.

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EFFETS CYTOTOXIQUES DE LA PROCAINE, DE LA LIGNOCAINE ET DE LA BUPIVACAINE

RESUME

On a étudié sur des cultures de fibroblastes de poumon de hampster chinois, les effets cytotoxiques de la procaine, de la lignocaine et de la bupivacaine. La croissance des cellules a été modérée pendant des expositions de 24 h à l'aide d'un ED_{50} de 0,17% pour la procaine, de 0,07% pour la lignocaine et de 0,02% pour la bupivacaine. La survie des cellules (mesurée suivant leur possibilité de former des colonies) a été diminuée pendant une exposition de 24 h à l'aide d'un ED_{50} de 0,21% pour la procaine, de 0,09% pour la lignocaine et de 0,06% pour la bupivacaine. Parmi les changements morphologiques citons la vacuolisation, l'arrondissement et la rétraction des cellules de la surface sur laquelle les cellules se développaient. La motilité a été ramenée à environ 50% des valeurs témoins par la lignocaine à 0,1%. Lorsque l'on a retiré les anesthésiques locaux, la croissance des cellules a repris après environ 15 h sans qu'il y ait eu des preuves de dommages aux chromosomes. Les changements correspondants provoqués par des inhalations d'agents anesthésiques ne se voient qu'à deux ou trois fois la concentration alvéolaire minimale requise pour l'anesthésie.

DIE ZYTOTOXISCHEN WIRKUNGEN VON PROCAIN, LIGNOCAIN UND BUPIVACAIN

ZUSAMMENFASSUNG

Die zytotoxischen Wirkungen von Procain, Lignocain und Bupivacain wurden anhand von Fibroblastkulturen aus den Lungen chinesischer Hamster studiert. Zellenwachstumshemmung trat ein, nachdem die Kulturen einer mittleren wirksamen Dosis von 0,17% fur Procain, 0,07% für Lignocain und 0,02% für Bupivacain über 24 Stunden ausgesetzt waren. Die Überlebensfahigkeit der Zellen (als Koloniebildungsfahigkeit gemessen) war reduziert, nachdem die Kulturen einer mittleren wirksamen Dosis von 0,21% für Procain, 0,09% fur Lignocain und 0,06% fur Bupivacain über 24 Stunden ausgesetzt waren. Die morphologischen Veranderungen umfassten Vakuolenbildung, Zellenabrundung und Retraktion von der Oberfläche, auf der die Zellen wuchsen. Die Bewegungsfähigkeit wurde durch 0,1% Lignocain auf ca. 50% der Kontrollkultur reduziert. Nach Entfernung der örtlichen Narkotika begann das Zellenwachstum nach ca. 15 Stunden wieder ohne nachweisbaren Chromosomschaden. Entsprechende, durch Inhalationsnarkotika herbeigefuhrte Veränderungen werden nur bei einer alveolaren Konzentration beobachtet, die zwei- bis dreimal höher ist als die für Anästhesie benotigte.

EFECTOS CITOTOXICOS DE PROCAINA, LIGNOCAINA Y BUPIVACAINA

SUMARIO

Se investigaron los efectos citotóxicos ejercidos por lignocaína, procaína y bupivacaína sobre cultivos de fibroblastos pulmonares del hamster chino. El crecimiento de las células fue inhibido durante exposiciones de 24 h con un ED_{50} de 0,17% para procaína, 0,07% para lignocaína y 0,02% para bupivacaína. La supervivencia celular (medida por su habilidad de former colonias) fue reducida durante la exposición de 24 h con un ED_{50} de 0,21% para procaína, 0,09% para lignocaína y 0,06% para bupivacaína. Los cambios morfológicos incluyeron vacuolación, redondeado y retracción de células de la superficie sobre la cual las células crecían. La movilidad fue reducida a aproximadamente 50% de la de control por lignocaína 0,1%. Al removerse las anestesias locales, el crecimiento de las células fue resumido al cabo de aproximadamente 15 h sin que se presentara evidencia de daño a los cromosomas. Los cambios correspondientes inducidos por anestesias de inhalación se producen solamente a dos o tres veces la concentración alveolar mínima necesaria para anestesia.

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EFFECT OF THE CHRONIC ADMINISTRATION OF NITROUS OXIDE 0.5% TO GRAVID RATS

E. VIEIRA

SUMMARY

Twenty-four gravid Wistar rats (12 experimental and 12 control) were studied. From day 1 to day 19 of gestation the experimental group was exposed day and night to nitrous oxide 0.5%, while the control group was exposed to air. On day 19 the rats were killed and a detailed examination of the uterus, ovaries and fetuses was undertaken. The fetuses were fixed, cleared and stained with alizarin red, examined for skeletal anomalies and their crown–rump lengths measured. There was a significant decrease in litter size of the dams exposed to nitrous oxide as compared with control ($P < 0.001$). Fetal resorption occurred in 10 of the 12 exposed dams. Skeletal anomalies were observed in 9% of the fetuses in the experimental group and there was an overall reduction in their size. None of the above changes were observed in the control.

There is increasing concern that anaesthetic gases, in the operating theatre and dental surgery atmosphere, may be hazardous to operating room personnel. Whilst the role of chronic exposure to anaesthetic agents has not been defined clearly, animal studies on the effect of prolonged exposure to high concentrations of nitrous oxide have shown that leucopaenia and embryo toxicity may be induced (Lassen et al., 1956; Green and Eastwood, 1963; Green, 1964; Corbett, 1972).

This study was undertaken to determine the effect of the continuous exposure of gravid rats to nitrous oxide 0.5% in air during their full period of gestation. This concentration was chosen to simulate the level of pollution approximately midway between that reported by Millard and Corbett (1974), and that observed in an unpublished investigation in our own institution.

MATERIALS AND METHODS

Two environmental chambers were constructed to hold commercial polypropylene rat cages. The chambers, each of 245 litre capacity, were supplied with compressed air at a flow rate of 35 litre min^{-1} provided by an oil-free diaphragm-type compressor. This ensured 8.5 air changes per hour. The rats were placed in modified cages having a base 35 cm × 35 cm with a mesh grid floor and a side 23 cm in height which contained a mesh grid side, opposite the gas delivery port, 18 cm × 11 cm. Three female rats were housed in each cage in an environmental chamber for a period of 7 days before commencing the study. At this point there were no male rats in the chambers. During this period only compressed air was supplied to the control and experimental chambers. At the commencement of the experiment nitrous oxide was added to the air supply of one chamber by means of a calibrated flow meter to provide a concentration of nitrous oxide 0.5% in air. Both gas supplies were mixed thoroughly by passage through a centrifugal fan before delivery to the chamber. The rats were fed on a standard laboratory ration and food and water were available *ad libitum* to all the rats during the acclimatization and experimental periods.

Initially, 30 Wistar Albino female nulliparous rats were selected randomly and placed in each chamber, breathing compressed air. The females were then mated in the chamber (breeding ratio: one male to four females). Each morning vaginal smears were screened microscopically for the presence of spermatozoa. Since mating in the rat occurs only during a short 12-h period of oestrus, evidence of mating may be used to indicate that conception has taken place (Nanda, 1969).

On the first night of breeding 12 females were found to have been mated, thus providing the total experimental group. These were transferred to the experimental chamber and nitrous oxide 0.5% was added to the air supply. This time was taken as day zero of the gestation period (Nanda, 1969). On the

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following 2 nights eight and four rats were mated respectively and were placed in the control chamber. The remaining non-pregnant rats were removed from the chamber. During the experimental period nitrous oxide, carbon dioxide and humidity were monitored by gas sampling and the concentrations detected with a katharometer in a Pye Unicam Gas Chromatograph calibrated as follows:

Column	2 m × ¼″ o.d. glass packed with Porapak; Q 80/100 mesh
Column temperature	80 °C
Injector temperature	150 °C
Detector	Thermal conductivity detector
Detector oven temperature	100 °C
Detector filament	150 °C
Carrier gas	Helium at 30 ml min^{-1}
Measurement of peaks	Peak areas: Pye Unicam DP88 computing integrator

In general the concentrations of nitrous oxide could be maintained within 0.46–0.50% in the four cages. The ventilation rate was investigated in a separate study, using nitrous oxide as a tracer gas. The air flow rate was reduced to 35 litre min^{-1} and nitrous oxide 175 ml min^{-1} was added to produce a 0.5% v/v mixture of nitrous oxide in air. The chamber was run for 1 h to stabilize the gas concentrations and the nitrous oxide supply was switched off. The decrease in nitrous oxide concentration in all four cages was monitored by simultaneous sampling of the air at 3-min intervals for 30 min. The decreasing concentrations of nitrous oxide recorded at the four levels in the chamber were comparable. After terminating the nitrous oxide supply the nitrous oxide concentration decreased to about one-half the original concentration in the first 7.5 min and by a little less than one-half again in the next 7.5 min. After 15 min of supplying air alone, only trace concentrations of nitrous oxide were detected in the air samples. These results indicate that at a flow rate of 35 litre min^{-1} (one air change per 7 min), a complete turnover of air occurred only every 14 min. This is attributed to the air flow pattern which was designed to produce air turbulence for mixing and even distribution of the supply. This mixing produced recirculation of air in the inhalation chamber. The persistence of trace concentrations of nitrous oxide would increase at the same rate if nitrous oxide was added to the air flow of 35 litre min^{-1}. On this basis it can be calculated that the concentrations of nitrous oxide are restored to their original values within 15 min when the chambers are returned to operation after the daily 10-min period when the environmental chambers were opened for sanitation and food and water replenishment.

Although no concentration gradients were found within the chambers, the positions of the cages were changed daily to randomize any unknown effects that the position of the cage might have had on the animals. No difference in the food and water consumption of the control and experimental rats was noted during the experimental period.

All the rats were killed on day 19 of the pregnancy by the administration of carbon dioxide in a lethal chamber. The abdominal viscera were exposed and a detailed examination of the ovaries and uterus was carried out using a dissecting microscope. The number of corpora lutea of pregnancy were counted by surface examination and compared with the number of fetuses present. When these numbers did not correspond, the uterus was examined for placentation sites and embryonic remnants, signs which indicated fetal resorption. The fetuses from each rat were counted, weighed and sexed by external characters: the male is characterized by a larger genital papilla and a greater distance between the anus and genital papilla. Each fetus was examined systematically for external malformations using a dissecting microscope. The body cavities were opened by a mid-ventral incision and a systematic examination of the internal organs was undertaken. The following organs were examined: head—palate, eyes, ears, nasal cavities; thorax—oesophagus, lungs, diaphragm, liver; abdomen—alimentary canal, kidneys, bladder.

The fetuses were fixed in 10% buffered formol saline and cleared in potassium hydroxide 0.5%, after which the fetal skeletons were stained with alizarin red. A systematic examination of the fetal skeletons was carried out in random order by placing the fetus on a light box and noting anatomical variations. The following were examined: skull, vertebral column, the ribs (counted and "wavy" ribs noted), fore limbs and hind limbs. When anatomical variations were found these were compared with litter mates and litters belonging to the control group.

Crown–rump measurements were taken using a modified version of the method described by van

Rensburg (1976). A steel pin was cemented to the floor of a Petri dish. To this pin a short length of 4/0 multi-filament stainless steel suture wire was fastened at one end to provide a measuring device. The alizarin-stained fetuses of the control and nitrous oxide-exposed groups were positioned so that the coronal suture wire was drawn along the mid-ventral dorsal surface of the fetuses and clamped with artery forceps at a point adjacent to the fourth coccygeal vertebrae. The wire was than straightened and the distance between the pin and artery forceps measured with Vernier calipers. This distance was taken as the crown–rump length of the fetus.

Statistical analyses

The experimental formula was a two-way nested design. The statistical analyses comprised an analysis of variance based on this design. The formulae were applied to the fetal weights and crown–rump measurements.

In the case of litter size, fetal resorption and skeletal malformation, the Student's *t* test, Chi-square test and Fisher's exact probability test were used respectively.

RESULTS

There was a total of 210 fetuses (133 control and 77 experimental). The mean number of rats per female is shown in table I. There were significantly fewer fetuses in the experimental dams ($P < 0.001$).

Varying degrees of fetal resorption were recorded in 10 of the 12 dams exposed to nitrous oxide. Four had resorption of all fetuses. No fetal death or resorption was found in any of the control dams. The Chi-square test applied to these results using a 2 × 2 contingency table revealed a significant difference between the groups ($P < 0.001$) (table I). Table II refers to the fetal observations in the control group.

No abnormalities of the internal organs were found, but skeletal anomalies were observed in 9% of the fetuses exposed to nitrous oxide. Fisher's exact probability test showed a significant P value < 0.05 for skeletal malformation between the control and nitrous oxide-exposed groups. The anomalies were mainly in the form of skeletal malformations. Malformations of the ribs were associated with scoliosis and kyphosis. No "wavy" ribs were observed. These fetuses were much smaller in size than their litter mates or fetuses from the control group.

TABLE I. *Fetal information in experimental group*

	Maternal rat number											
	1	2	3	4	5	6	7	8	9	10	11	12
Live fetuses	7	9			13			11	11	10	5	11
Resorption sites	4	1	11	12	2	10	12		1			
Fetal weight (g): Mean	1.44	1.33			1.80			1.28	1.46	1.66	1.82	2.05
± SD	0.21	0.20			0.04			0.25	0.15	0.05	0.20	0.08
Crown–rump length (mm): Mean	29	28			30			29	28	28	28	29
± SD	0.20	0.20			0.21			0.22	0.20	0.21	0.22	0.20
Live fetuses with abnormalities		1			2			1	1	2		2
Number of live fetuses without abnormality	7	8			11			10	10	8	5	9

TABLE II. *Fetal information in control group. (No fetal abnormality or resorption were found)*

	Maternal rat number											
	1	2	3	4	5	6	7	8	9	10	11	12
Live fetuses	12	12	10	10	10	13	12	12	9	13	12	10
Fetal weight (g): Mean	2.0	3.5	3.1	3.3	3.1	3.2	2.6	2.0	2.0	2.0	2.3	2.3
± SD	0.10	0.21	0.04	0.55	0.21	0.31	0.33	0.21	0.13	0.14	0.22	0.21
Crown–rump length (mm): Mean	44	44	44	43	42	42	44	44	42	43	44	44
± SD	0.20	0.22	0.21	0.20	0.20	0.21	0.22	0.20	0.21	0.22	0.20	0.22

There was a marked reduction in the mean crown–rump length of the fetuses exposed to nitrous oxide. An analysis of variance of the two groups showed the difference to be significant ($P < 0.001$) (table I).

The difference in mean body weight between the two groups was significant ($P < 0.001$) (table I).

Of the fetuses exposed to nitrous oxide, there were 29 males and 48 females (control 64 males and 69 females). Of the 48 female fetuses in the experimental group, 10 had skeletal anomalies whilst only one male in this group showed a similar malformation. This higher prevalence of malformation in female fetuses was significant only at the 5% level.

DISCUSSION

The conditions of experimental exposure to nitrous oxide in air mixtures which have been reported vary considerably. Fink, Shepard and Blandau (1967) reported skeletal malformations in fetuses of gravid rats exposed continuously to 50% nitrous oxide for 2, 4 and 6 days. Ramazoto, Katz and Cupiola (1975) studied the effect of exposures to 50% nitrous oxide for 25 min per day at various stages of pregnancy in the rat. They found that this caused an increase in the fetal death rate.

Most previous studies have used concentrations of nitrous oxide that might be administered to patients undergoing anaesthesia whilst the present study has been designed specifically to determine the biological effects, on fetal development, of concentrations of nitrous oxide in the atmospheric pollution range.

The reduction in fetal number per rat in this study was associated with fetal death and resorption. This observation was confirmed by the fact that the numbers of corpora lutea of pregnancy recorded in the ovaries of rats with fetal resorption corresponded exactly to the number of implantation sites found in the uterine horns. These results support the finding of Ramazotto, Katz and Cupiola (1975) and Vieira and colleagues (1976) that nitrous oxide may be lethal to the rat fetus. The decrease in body weight observed in the fetuses which survived in the dams exposed to nitrous oxide, together with the significant reduction in the crown–rump measurements of the same fetuses, complements the observations by Vieira and colleagues (1976) that prenatal exposure of gravid rats to this gas reduced the postnatal growth of their offspring. This indicates that nitrous oxide retards growth in young rats.

The nitrous oxide 0.5% in air mixture produced also abnormalities of the vertebrae and ribs. Similar observations were recorded by Fink, Shepard and Blandau (1967) using a concentration of nitrous oxide 50% in air.

The reason for the difference in prevalence of skeletal abnormalities in the male and female fetuses is not clear. Fink, Shepard and Blandau (1967) made similar observations on the lethal effect of nitrous oxide on male fetuses. It would appear that male fetuses may be more susceptible to nitrous oxide than females.

Three conclusions may be drawn from the present study. First, the continuous exposure of gravid dams to a nitrous oxide 0.5% in air mixture produced fetal death, skeletal abnormalities and prenatal growth retardation. Whilst these results cannot be extrapolated directly to man, caution should be exercised until the specific biological effects of long exposure to low concentrations of nitrous oxide have been determined.

Second, there is a varying susceptibility of fetuses to nitrous oxide and, finally, the Wistar rat is a good experimental model for studies on nitrous oxide pollution.

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EFFET DE L'ADMINISTRATION CHRONIQUE DE PROTOXYDE D'AZOTE A 0,5% A DES RATES PLEINES

RESUME

On a procédé à une étude sur 24 rates Wistar gravides (12 à titre expérimental; 12 comme témoins). Du premier jour de la gestation au 19e jour, le groupe expérimental a été exposé nuit et jour à du protoxyde d'azote à 0,5% alors que le groupe témoin a été exposé à l'air. Le 19e jour, les rates ont été tuées et on a effectué un examen détaillé de l'utérus, des ovaires et des fœtus. Les fœtus ont été fixés, dégagés et teintés de rouge d'alizarine, puis examinés pour détecter les anomalies aux squelettes; on a ensuite mesuré la distance de leurs têtes à leurs croupes. Il y a eu une réduction importante dans la taille de la portée des mères qui avaient été exposées au protoxyde d'azote, par comparaison aux animaux témoins ($P<0{,}001$); la résorption du fœtus s'était produite chez 10 mères sur les 12 qui y avaient été exposées. Des anomalies du squelette ont été observées sur 9% des fœtus du groupe expérimental et on a constaté une diminution générale dans leur taille. Aucune de ces modifications n'a été observée sur les animaux témoins.

WIRKUNG DER CHRONISCHEN VERABREICHUNG VON 0,5% STICKOXYD AN GRAVIDE RATTEN

ZUSAMMENFASSUNG

Vierundzwanzig gravide Wistar-Ratten (12 experimentell und 12 als Kontrolle) wurden untersucht. Von Tag 1 bis Tag 19 der Schwangerschaft wurde die experimentelle Gruppe Tag und Nacht 0,5% Stickoxyd ausgesetzt, während die Kontrollgruppe Luft atmete. Am Tag 19 wurden die Ratten getötet und Uterus, Eierstocke und Fötus genau untersucht. Der Fötus wurde in allen Fällen fixiert, freigemacht und mit Alizarinrot gefärbt, auf Skelettanomalien untersucht und die schwanzlose Länge gemessen. Die dem Stickoxyd ausgesetzten Ratten hatten einen viel kleineren Wurf wie die aus der Kontrollgruppe ($P<0{,}001$). Foetale Resorption erfolgte bei 10 der 12 Stickoxyd-Ratten. Skelettanomalien wurden bei 9% der Föten der experimentellen Gruppe beobachtet, bei denen auch eine allgemeine Grössenverringerung der Fall war. Keine der obigen Veränderungen wurde in der Kontrollgruppe festgestellt.

EFECTO EJERCIDO POR LA ADMINISTRACION CRONICA DE OXIDO NITROSO 0,5% A RATAS GRAVIDAS

SUMARIO

Se estudiaron 24 ratas Wistar (12 experimentales y 12 de control). Desde el día 1 hasta el día 19 de gestación, el grupo experimental fue expuesto día y noche a 0,5% de oxido nitroso, mientras que el grupo de control fue expuesto al aire. El día 19 las ratas fueron muertas, realizándose un examen detenido de los úteros, ovarios y fetos. Los fetos fueron fijados, limpiados y manchados con colorante de alizarina, examinados en busca de anormalidades del esqueleto y se midió la longitud entre coronilla-anca. Hubo una significativa disminución en en número de crías que nacieron de las madres expuestas a oxido nitroso, en comparación con las de control ($P<0{,}001$). La reabsorción fetal ocurrió en 10 de las 12 madres expuestas. Se observaron anormalidades esqueléticas en 9% de los fetos en el grupo experimental y una reducción general en su tamaño. Ninguno de los mencionados cambios fueron observados en el grupo de control.

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EFFECT OF HYPERCARBIA ON HEPATIC BLOOD FLOW AND OXYGEN CONSUMPTION IN THE GREYHOUND

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SUMMARY

The stability of a technique for measuring hepatic blood flow and oxygen consumption was established in six greyhounds anaesthetized with pentobarbitone (group A). Subsequently, the effects of increased Pa_{CO_2} were studied in another six animals (group B). With one exception (splenic blood flow) no significant changes were observed in any of the indices measured in group A. In group B, although hepatic arterial blood flow (HABF) decreased when Pa_{CO_2} increased, both portal venous blood flow (PVBF) and total liver blood flow (HABF+PVBF) increased. However, these changes were much less marked after 20 min. Hepatic oxygen consumption and splenic venous blood flow were unchanged with an increase in Pa_{CO_2}.

Despite major advances in hepato–biliary surgery in recent years, knowledge of the effects of anaesthetic agents on hepatic arterial and portal venous blood flows and hepatic oxygen consumption is limited (Goldberg, 1970; Batchelder and Cooperman, 1975; Cooperman, Wollman and Marsh, 1977). In addition, data on the effect of increased arterial carbon dioxide tensions on hepatic blood flow are contradictory, some authors suggesting it increases flow (Scholtholt and Shiraishi, 1970) and some that it decreases flow (Epstein et al., 1961; Cooperman, 1972; Juhl and Einer-Jensen, 1977). It was thought desirable, therefore, to make use of more recently available technology in an attempt to clarify the situation.

We have devised an animal model for studying the hepatic circulation and have used it to examine the effects of increases in arterial carbon dioxide tension on hepatic blood flow and oxygen consumption.

MATERIALS AND METHODS

The animal model

Anaesthesia was induced in greyhounds (wt 25–35 kg) with thiopentone 20 mg kg^{-1} i.v. and maintained with pentobarbitone 30 mg kg^{-1} initially and supplements of 2 mg kg^{-1} i.v. if required later in the investigation. Following tracheal intubation, the lungs were ventilated artificially (Barnet Mk II ventilator) with a mixture of nitrogen 75% in oxygen. The minute volume and the inspired oxygen concentration were adjusted to maintain normal Pa_{CO_2} and Pa_{O_2} tensions. Pancuronium 0.15 mg kg^{-1} was administered to produce neuromuscular blockade.

Following laparotomy, the hepatic artery (HA) was dissected free of adventitiae, for a distance of 1 cm, at a site 1–2 cm from the coeliac axis. The nerve plexus was left intact. A 3-mm electromagnetic flow (e.m.f.) probe (Statham) was applied and flow was measured with Statham 2202 flow meters. The gastroduodenal artery and the right gastric artery were ligated to ensure that true hepatic arterial flow was measured. A 1-cm length of the portal vein (PV) was dissected, proximal to the insertion of the gastroduodenal vein, and a 6-mm e.m.f. probe applied. The gastroduodenal vein was ligated distal to the point of insertion of a cannula, the tip of which was at the junction of the gastroduodenal vein and the portal vein. This cannula was used to sample portal venous blood, to record portal venous pressure and as an injection site for xenon-133 solution (fig. 1). A portion of the splenic vein was exposed distal to its junction with the left gastric vein and a 3-mm e.m.f. probe was applied (the spleen was not removed). The hepatic vein (HV) was cannulated via the external jugular vein and the position of the tip of the catheter within an hepatic vein was confirmed by direct palpation. This was used for measurement of hepatic venous pressure and sampling of hepatic venous blood.

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Systemic arterial pressure was recorded in the abdominal aorta via a cannula inserted via the right femoral artery. A thermistor-tipped, triple-lumen catheter was passed via the right femoral vein into a pulmonary artery and cardiac output was measured by the thermal dilution technique (Forrester et al., 1972). In addition, core temperature was monitored and was maintained at 38 °C by means of heating lamps.

Hepatic tissue blood flow was determined by external scintillation counting over the liver following the injection of 1.0–1.5 mCi of xenon-133 solution into the gastroduodenal vein (MacKenzie et al., 1976). Flow was calculated from the fast component of the clearance curve (Mathie et al., 1978). Hepatic oxygen consumption was calculated as follows:

Hepatic oxygen consumption (ml min^{-1}) =

$$\left(\frac{\text{PVBF}}{100}\times(\text{PV}-\text{HV})\ \text{O}_2\ \text{content}\right)+\left(\frac{\text{HABF}}{100}\times(\text{HA}-\text{HV})\ \text{O}_2\ \text{content}\right)$$

where PV and HA blood flow is in ml min^{-1}.

The portal venous, hepatic arterial and hepatic venous oxygen contents were measured using the Lex-O_2-Con electrolytic cell (Lexington Instruments) (Kusumi, Butts and Ruff, 1973).

Blood-gas tensions and pH measurements were made using appropriate, suitably calibrated electrodes (Corning). Since it appears that dogs maintain normally a compensated metabolic acidosis (Zweens et al., 1977), the base deficit was maintained at −4 mmol litre^{-1} by the administration of sodium bicarbonate when required. In addition, liver function tests and measurements of the concentrations of the plasma electrolytes were undertaken at the beginning and at the end of each investigation. In those animals subjected to increases in arterial carbon dioxide tension (see below) the haematocrit was measured before and during each step increase in Pa_{CO_2}. Throughout each investigation the fluid balance of the animal was maintained by the i.v. infusion of 0.9% sodium chloride 15 ml kg^{-1} h^{-1}.

Experimental programme

Control animals (group A). To assess the stability of the preparation, six animals were prepared surgically as described above (approximately 3 h elapsed between the induction of anaesthesia and the termination of surgery). Subsequently, control conditions were maintained and measurements made at hourly intervals for 3 h.

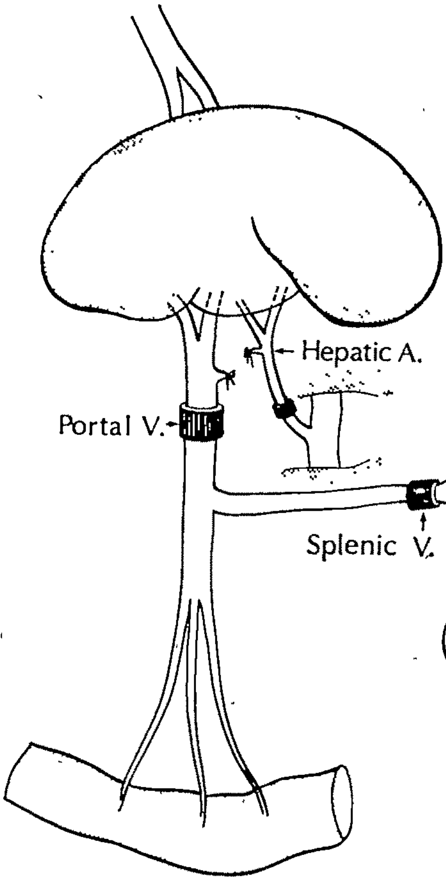

FIG. 1. Diagrammatic illustration of the sites of application of the portal venous, hepatic arterial and splenic venous electromagnetic flow probes. Ligatures are applied to the cut ends of the gastroduodenal artery and vein.

Hypercarbia animals (group B). In another six animals, following the determination of the baseline values, carbon dioxide was added to the inspired gas mixture and measurements performed at Pa_{CO_2} values of approximately 7.3 kPa, 9.3 kPa, 11.3 kPa and 13.3 kPa. Each value of Pa_{CO_2} was maintained for 30–40 min and, since the response was found to be biphasic, measurements were obtained at both 2–3 min and approximately 20–30 min. Pa_{CO_2} returned to its baseline value (5.3 kPa) between each step change.

Analysis of results

Mean arterial pressure has been calculated as the arterial diastolic pressure plus 1/3 pulse pressure. The

TABLE I. *Results (mean ± SEM) obtained in six control animals (group A) over a 3-h period. Significant difference from the initial value:* * $P < 0.05$

	Control	1 h	2 h	3 h
Mean arterial pressure (mm Hg)	125.8 ± 10.0	132.7 ± 9.3	134.3 ± 10.1	135.0 ± 10.3
Cardiac output (litre min^{-1} kg^{-1})	0.193 ± 0.012	0.191 ± 0.0[illegible]9	0.188 ± 0.009	0.203 ± 0.019
Portal venous blood flow (ml 100 g^{-1} min^{-1})	116.8 ± 10.9	115.4 ± 10.[illegible]	113.1 ± 8.3	121.2 ± 11.9
Hepatic arterial blood flow (ml 100 g^{-1} min^{-1})	33.5 ± 7.3	32.3 ± 7.7	29.1 ± 4.9	28.6 ± 6.4
Total liver blood flow (HABF + PVBF) (ml 100 g^{-1} min^{-1})	150.3 ± 11.0	147.7 ± 9.9	142.2 ± 8.2	149.8 ± 12.2
TLBF (xenon-133) (ml 100 g^{-1} min^{-1})	156.8 ± 8.7	148.8 ± 15.[illegible]	139.3 ± 8.7	159.3 ± 14.9
Splenic venous blood flow (ml min^{-1} kg^{-1})	4.04 ± 0.78	3.60 ± 0.57	3.20 ± 0.59*	3.24 ± 0.6
Hepatic oxygen consumption (ml 100 g^{-1} min^{-1})	3.32 ± 0.70	3.70 ± 0.60	3.63 ± 0.33	3.52 ± 0.56
Portal venous pressure (mm Hg)	7.30 ± 0.93	7.35 ± 0.8[illegible]	7.60 ± 1.14	8.30 ± 1.1

significance of differences between the baseline values and the later values was assessed using Student's *t* test for paired data.

The analysis in group A (table I) was made in each case with reference to the control values at the start of the measurements.

The analysis in group B (table II) was performed using the absolute values quoted with reference to each immediately preceding normocapnic control value as shown in table II.

RESULTS

Control animals (group A)

With the exception of the splenic blood flow at 2 h, all the measurements obtained in the six dogs in this group remained stable throughout the period of study (table I).

Hypercarbia (group B)

The mean arterial pressure decreased significantly at Pa_{CO_2} values of 9.3, 11.3 and 13.3 kPa and there was no difference in the values obtained 2–3 or 20 min after administration of carbon dioxide. Cardiac output (measured only at 20 min) increased with increasing Pa_{CO_2} and the change was significant with Pa_{CO_2} of 13.3 kPa (table II).

Hepatic arterial blood flow decreased significantly at all Pa_{CO_2} values immediately on administration of the carbon dioxide, but by 20 min the decreases were significant only at Pa_{CO_2} 11.3 kPa (figs 2, 3). Likewise, the portal venous blood flow increased significantly with increased Pa_{CO_2} in the initial measurements, but by 20 min the increases were significant only at Pa_{CO_2} 11.3 and 13.3 kPa (figs 2, 3). The changes in portal venous flow were greater than those in hepatic arterial flow and, as a result, total liver blood flow (the sum of the two) increased significantly at 11.3 and 13.3 kPa immediately and remained increased at the 13.3-kPa tension after 20 min (figs 2, 3).

Changes in total liver perfusion, measured by xenon clearance 20 min after the addition of carbon dioxide were similar to those in total liver blood flow using the e.m.f. technique. The correlation between the two methods of measurement was highly significant ($r = 0.81$; $n = 50$; $P < 0.001$). Hepatic oxygen consumption 20 min after the addition of carbon dioxide did not change significantly from the control. However, hepatic venous oxygen content increased significantly at Pa_{CO_2} 13.3 kPa (table II).

Changes in the concentrations of sodium, chloride and potassium were small and the only significant alteration in the liver function tests was an increase in aspartate transaminase concentration.

DISCUSSION

Throughout these investigations, background anaesthesia was provided with pentobarbitone, which has

TABLE II. *Results (mean ± SEM) obtained in six animals (group B) subjected to increases in* Pa_{CO_2} (7.3, 9.3, 11.3, 13.3 *kPa*). *Results obtained immediately before each administration of carbon dioxide (a) and 2–3 min (b) and 20 min (c) after commencement of the administration are presented. Significant differences from values obtained at (a):* * $P < 0.05$, ** $P < 0.01$

	7.3 kPa			9.3 kPa		
	a	b	c	a	b	c
Mean arterial pressure	109	111	111	118	107*	106*
(mm Hg)	±8.9	±9.8	±10.2	±10.6	±10.6	±10.2
Cardiac output	0.148		0.147	0.140		0.156
(litre min^{-1} kg^{-1})	±0.008		±0.011	±0.007		±0.012
Portal venous blood flow	115.3	126.0	115.0	99.5	116.0*	113.0
(ml 100 g^{-1} min^{-1})	±11.0	±16.7	±14.0	±10.6	±13.5	±14.3
Hepatic arterial blood flow	22.3	16.1*	17.1	20.2	12.1**	15.7
(ml 100 g^{-1} min^{-1})	±4.1	±3.3	±3.1	±4.2	±2.8	±3.7
Total liver blood flow	137.6	142.1	132.1	119.7	128.1	128.7
(HABF+PVBF)	±15.9	±17.6	±17.8	±11.8	±14.7	±16.3
(ml 100 g^{-1} min^{-1})						
TLBF (xenon-133)	129.5	—	124.5	—	—	134.2
(ml 100 g^{-1} min^{-1})	±15.0		±14.5			±11.8
Splenic venous blood flow	5.89	—	5.56	4.83	—	4.92
(ml min^{-1} kg^{-1})	±2.22		±3.39	±1.86		±3.58
Hepatic oxygen consumption	5.74	—	6.33	5.60	—	4.93
(ml 100 g^{-1} min^{-1})	±0.65		±0.78	±1.70		±0.42
Hepatic venous O_2 content	15.6	—	17.1	15.9	—	17.1
(ml dl^{-1})	±1.9		±1.6	±1.9		±1.5
Portal venous pressure	8.7	—	10.7*	10.0	—	12.0
(mm Hg)	±1.8		±1.7	±2.2		±2.8
Haematocrit	0.50	—	0.54	0.53	—	0.55
	±0.03		±0.04	±0.03		±0.03

	11.3 kPa			13.3 kPa		
	a	b	c	a	b	c
Mean arterial pressure	117	102*	102*	118	102**	97**
(mm Hg)	±11.8	±11.8	±10.6	±11.4	±11.0	±11.0
Cardiac output	0.140		0.160	0.164		0.182*
(litre min^{-1} kg^{-1})	±0.013		±0.018	±0.014		±0.017
Portal venous blood flow	84.2	124.0**	107.0*	91.2	139.0*	113.1*
(ml 100 g^{-1} min^{-1})	±11.9	±19.6	±18.8	±15.9	±22.9	±27.3
Hepatic arterial blood flow	21.5	11.2**	15.9*	23.7	10.5*	16.9
(ml 100 g^{-1} min^{-1})	±3.6	±2.2	±3.3	±3.9	±1.9	±3.1
Total liver blood flow	105.7	135.2**	123.9	114.9	149.5*	130.0*
(HABF+PVBF)	±12.7	±18.8	±18.8	±15.9	±22.0	±24.6
(ml 100 g^{-1} min^{-1})						
TLBF (xenon-133)	—	—	134.8	—	—	144.2
(ml 100 g^{-1} min^{-1})			±13.4			±14.0
Splenic venous blood flow	4.41	—	4.70	4.80	—	4.34
(ml min^{-1} kg^{-1})	±2.10		±2.36	±2.23		±2.37
Hepatic oxygen consumption	4.86	—	5.62	5.85	—	6.0
(ml 100 g^{-1} min^{-1})	±2.13		±1.22	±3.41		±2.81
Hepatic venous O_2 content	17.1	—	17.3	15.9	—	18.1*
(ml dl^{-1})	±1.8		±1.3	±1.4		±1.5
Portal venous pressure	9.8	—	12.4	11.6	—	14.3*
(mm Hg)	±2.6		±1.8	±2.8		±2.9
Haematocrit	0.52	—	0.56*	0.53	—	0.57*
	±0.02		±0.03	±0.03		±0.03

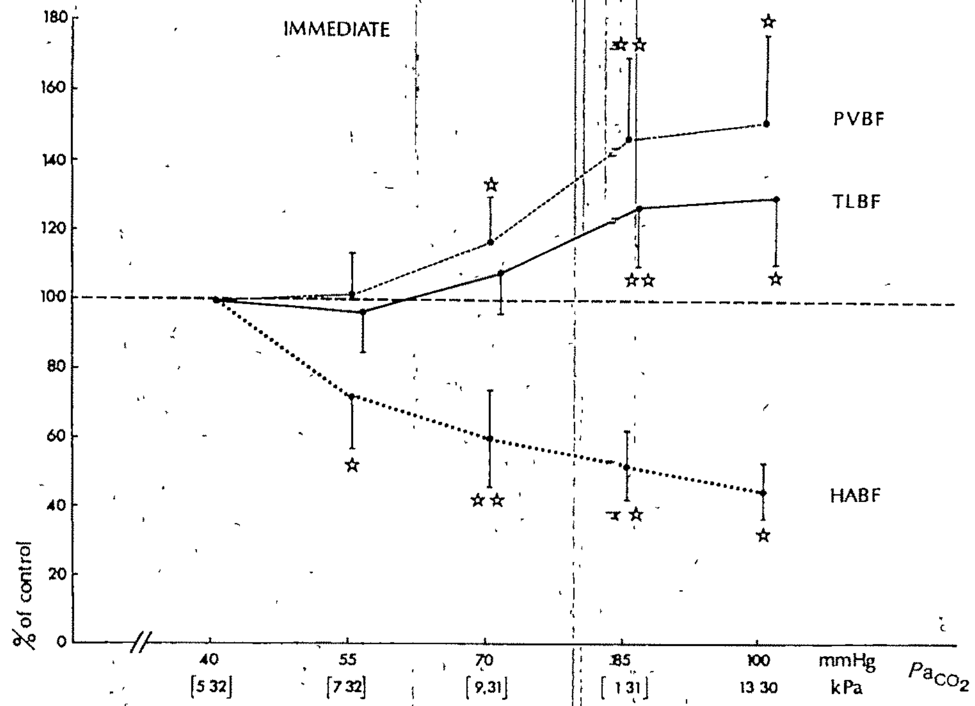

FIG. 2. The effects of four tensions of carbon dioxide upon total liver blood flow (TLBF), portal venous blood flow (PVBF) and hepatic arterial blood flow (HABF) immediately after the administration of carbon dioxide. The values are shown as percentages of each preceding control value expressed as 100%; bars indicate ± SEM; * $P < 0.05$, ** $P \leq 0.01$. (The analysis was performed upon absolute values in table II.)

been shown previously to produce stable cardiovascular conditions in the dog (Gilmore, 1965), and to have no significant effect upon liver blood flow in that animal (Fischer et al., 1956; Gilmore, 1958; Evringham, Brenneman and Horvath, 1959). The only significant change noted in control measurements (group A, table I) was a 20% decrease in splenic blood flow probably associated with handling. While, completely stable control conditions could be produced, in theory, by the use of an isolated perfused liver, this particular preparation has proved to be very difficult to use because of the histamine-mediated hepatic outflow block syndrome (Dionigi and Alexander, 1970; Greenway and Stark, 1971).

Electromagnetic flow meters have been used for nearly 20 years to measure hepatic arterial and portal venous blood flows (Drapanas, Kluge and Schenk, 1960). However, the study of liver blood flow in the dog has been made especially difficult by the necessity, with earlier flow meters, to occlude the portal vein mechanically—a procedure which rapidly produces shock in this species. A further difficulty resulted from the proximity of the hepatic arterial and portal venous e.m.f. probes, because of interference between the two magnets. The Statham 2202 flow meter avoids these problems. The ability to monitor blood flow continuously was especially valuable in this study where a biphasic action of carbon dioxide on hepatic arterial and portal venous blood flows was shown. A verification of the accuracy of this method of measurement has been provided by the authors' comparison with the xenon-133 clearance technique both in this study and in a previous report (Mathie et al., 1978).

Although there were no significant changes in oxygen consumption at any stage of the study, at Pa_{CO_2} 13.3 kPa, hepatic venous oxygen content increased significantly suggesting that, in the steady state, carbon dioxide does not affect oxygen consumption by the liver and, in view of the increased blood flow, may be beneficial.

It was noticeable that both the immediate increase in portal blood flow and the immediate decrease in hepatic arterial blood flow in response to carbon dioxide diminished towards baseline values over the

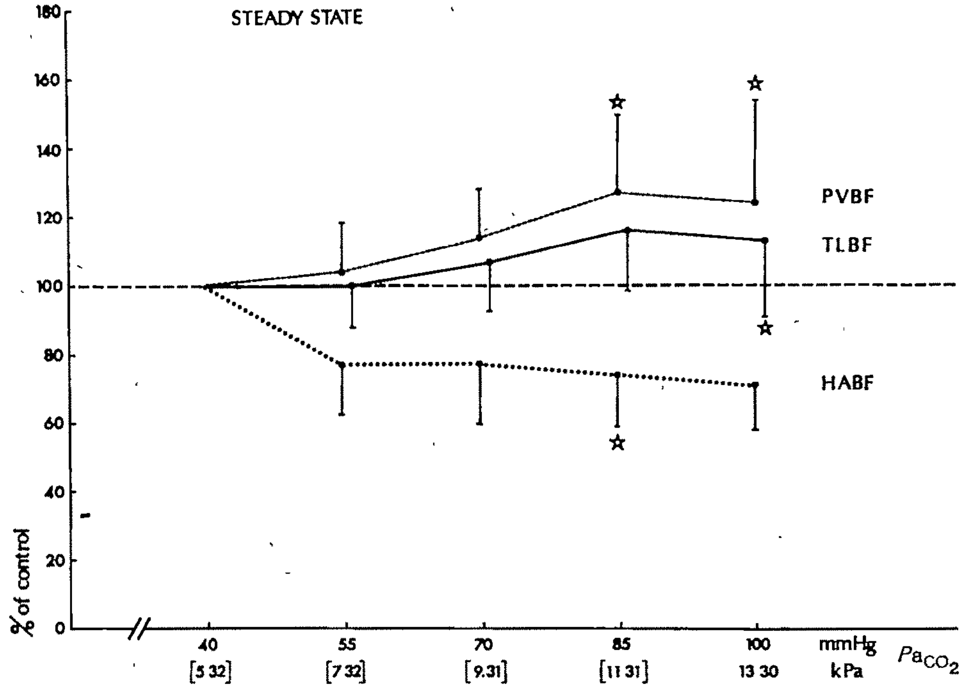

FIG. 3. The effects of four tensions of carbon dioxide upon total liver blood flow (TLBF), portal venous blood flow (PVBF) and hepatic arterial blood flow (HABF) after a 20 min administration of carbon dioxide. The values are shown as percentages of each preceding control value expressed as 100%; bars indicate ±SEM; * $P < 0.05$. (The analysis was performed upon absolute values in table II.)

course of the subsequent 20 min of administration. It appears that the initial effect of carbon dioxide was direct vasodilatation and, subsequently, a sympathetically mediated vasoconstriction may have developed (Manley, Nash and Woodbury, 1964), causing a decrease in flow towards baseline. It seems likely that the initial decrease in hepatic arterial blood flow was not a direct effect of carbon dioxide but could be a mechanical phenomenon caused by the increase in portal vein and sinusoidal pressure, thereby impeding hepatic arterial flow.

This hypothesis is supported by the demonstration that small increases in hepatic venous pressure, resulting in increases in portal venous pressure similar to those seen in this investigation, result in a marked decrease in hepatic arterial blood flow (Ternberg and Butcher, 1965; Hanson and Johnson, 1966; Lutz, Peiper and Bauereisen, 1968).

The increase in liver flow with carbon dioxide seen in this study confirms previous results (Tashkin, Goldstein and Simmons, 1969; Scholtholt and Shiraishi, 1970), obtained with e.m.f. probes. However, other workers (Epstein et al., 1961; Juhl and Einer-Jensen, 1977) have shown a decrease in splanchnic blood flow with hypercarbia. Our experiments have shown that the changes in flow vary considerably over a 20-min period and it may be that conflicting results may be explained by the use of different periods of administration of carbon dioxide before measurement of liver blood flow. The discrepancies could also be a result of differences in measurement techniques, species and anaesthesia.

In this study there was a progressive decrease in the baseline values for portal venous blood flow after each administration of carbon dioxide. Our control series demonstrated that portal venous blood flow remains stable in this preparation if it is not exposed to carbon dioxide. This would suggest that the secondary decrease in portal venous blood flow seen with carbon dioxide administration persists after withdrawal of the gas, resulting in the decreased baseline values.

It has been shown that severe hypercapnia (30% carbon dioxide) produced splenic contraction

(Ramlo and Brown, 1959) and, as it was considered of value to see if changes in splenic blood flow markedly affected portal flow, splenic blood flow was measured. No significant changes were seen and this demonstrates that at these tensions of carbon dioxide the spleen plays no role in the changes in portal blood flow. However, small but significant increases in haematocrit were seen, suggesting that a degree of splenic contraction, too small to affect flow, must be occurring.

Since the mean arterial pressure decreased at carbon dioxide tensions of 9.3 kPa and above and the cardiac output was noted to have increased at the higher tensions, it can be inferred that the smooth muscle relaxant effect of carbon dioxide on peripheral blood vessels (Price, 1960) predominated over central sympathetic stimulation.

In conclusion, it is felt that this particular animal model has been shown to be stable and suitable for studies on the hepatic circulation. Our data demonstrated that carbon dioxide produced an increase in liver blood flow without affecting oxygen consumption. This effect could prove valuable in a liver with a compromised blood supply. Furthermore, we feel that this model will prove valuable in further studies of the effects of alterations of blood-gas tensions and of the influence of anaesthetic agents on the hepatic circulation.

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EFFET DE L'HYPERCARBIE SUR LE DEBIT SANGUIN HEPATIQUE ET SUR LA CONSOMMATION D'OXYGENE CHEZ LE LEVRIER

RESUME

On a déterminé la stabilité d'une technique permettant de mesurer le débit sanguin hépatique et la consommation d'oxygène, sur six lévriers anesthésiés au pentobarbitone (Groupe A). On a étudié par la suite, les effets de l'augmentation de la Pa_{CO_2} sur six autres animaux (Groupe B). A une exception près (débit sanguin splénique) on n'a observé aucun changement important dans aucun autre des indices mesurés sur le Groupe A. En ce qui concerne le Groupe B, bien que le débit sanguin artériel hépatique (HABF) ait diminué lorsque la Pa_{CO_2} a augmenté, le débit sanguin de la veine porte (PVBF) et la totalité du débit sanguin du foie (HABF+PVBF) ont augmenté. Après 20 min, ces changements ont été nettement moins marqués. La consommation d'oxygène du foie et le débit sanguin veineux splénique sont demeurés sans changement lors de l'augmentation de la Pa_{CO_2}.

DIE WIRKUNG EINES ÜBERMÄSSIG HOHEN KOHLENSÄUREGEHALTS IM BLUT AUF DEN LEBERBLUTFLUSS UND DEN SAUERSTOFFVERBRAUCH IM WINDHUND

ZUSAMMENFASSUNG

Es wurde die Stabilitat eines Messverfahrens fur den Leberblutfluss und Sauerstoffverbrauch in sechs, mit Pentabarbiton narkotisierten Windhunden (Gruppe A) festgestellt. Danach wurde die Wirkung eines erhohten Pa_{CO_2} in weiteren sechs Tieren studiert (Gruppe B). Mit einer Ausnahme (Milzblutfluss) wurden in keinem der gemessenen Indexe in Gruppe A bedeutsame Veränderungen beobachtet. Obwohl in Gruppe B der arterielle Leberblutfluss (HABF) mit Anstieg des Pa_{CO_2} abnahm, nahmen hier sowohl der Pfortaderblutfluss (PVBF) als auch der Gesamtblutfluss der Leber (HABF+PVBF) zu. Nach 20 Min jedoch waren diese Veränderungen viel weniger ausgeprägt. Der hepatische Sauerstoffverbrauch und der Milzaderblutfluss blieben bei einem Pa_{CO_2}-Anstieg unverändert.

EFECTO EJERCIDO POR HIPERCARBIA SOBRE LA CIRCULACION DE SANGRE HEPATICA Y EL CONSUMO DE OXIGENO EN EL GALGO

SUMARIO

Se determinó la estabilidad de una técnica para medir la circulación de sangre hepática y el consumo de oxígeno en seis galgos anestesiados con pentobarbitona (Grupo A). Posteriormente, se estudiaron los efectos ejercidos por el aumento de Pa_{CO_2} en otros seis animales (Grupo B). Con una sola excepción (circulación de sangre esplénica), no se observaron cambios significativos en ninguno de los índices medidos en el grupo A. En el grupo B, aunque la circulación de sangre arterial hepática (HABF) disminuyó al aumentar el Pa_{CO_2}, aumentó la circulación de sangre venosa portal (PVBF) y la circulación de sangre total en el hígado (HABF+PVBF). Sin embargo, estos cambios fueron mucho menos marcados al cabo de 20 min. El consumo de oxígeno hepático y la circulación de sangre venosa esplénica continuaron sin cambio ante el aumento de Pa_{CO_2}.

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EFFECT OF HYPOTENSION INDUCED WITH SODIUM NITROPRUSSIDE ON CANINE CORONARY ARTERIAL FLOW

J. P. VANCE, D. M. BROWN, G. SMITH AND J. THORBURN

SUMMARY

In seven dogs anaesthetized with pentobarbitone, coronary and pulmonary artery blood flows were measured using electromagnetic flow meters. The infusion of a 0.01% solution of sodium nitroprusside caused an initial small increase in mean coronary artery flow which returned to control as the arterial pressure decreased. No changes were noted in cardiac output nor were further changes observed in coronary flow. Heart rate was increased consistently during the hypotension and left ventricular d*p*/d*t* max was reduced as were coronary and total peripheral resistances. There were no significant changes in myocardial or total body oxygen extraction or consumption.

Arterial pressure is an important factor in determining the blood flow through any vascular bed. Since the arterial pressure in the coronary vascular bed is virtually identical with aortic pressure, factors which influence aortic pressure might be expected to affect flow in the coronary vasculature. This has been shown to be the case in haemorrhagic hypotension (Ledingham et al., 1971) and hypotension induced with halothane (Smith et al., 1974).

This investigation was carried out to determine if decreases in the arterial pressure produced by the infusion of sodium nitroprusside had an effect on coronary arterial flow.

METHODS

Seven healthy adult dogs (six greyhounds and one other) whose weights ranged between 25 and 31 kg were anaesthetized with pentobarbitone sodium 30 mg kg^{-1} i.v. Endotracheal intubation was performed once neuromuscular blockade had been achieved with suxamethonium 50 mg i.v. or i.m. Ventilation of the lungs was controlled (Palmer large animal ventilator) and the minute volume was adjusted to provide Pa_{CO_2} of approx. 5.3 kPa. The mixture of the ventilating gas (nitrogen in oxygen) was adjusted to produce Pa_{O_2} of approx. 13.3 kPa. During the investigation suxamethonium 50 mg i.m. was given as required to abolish reflex movement (usually about every 45 min).

With the animal in the right lateral position, catheters were inserted under radiographic control, into the coronary sinus via the left internal jugular vein and into the right atrium via the right femoral vein. A third catheter was passed via the right femoral artery, into the descending thoracic aorta. The right atrial and aortic catheters were connected to appropriate transducers for pressure recording. A copper–constantan thermocouple was passed into the oesophagus to the level of the heart and e.c.g. limb leads were attached by needle electrodes.

A left thoracotomy was performed and a short segment (1–2 cm) of either the circumflex or the anterior descending branch of the left coronary artery was dissected.

A 2.0-mm or 2.5-mm flow transducer (Statham SP7515) was applied to the cleared segment of artery so that a close fit was obtained. The pulmonary artery was separated from the arch of the aorta by carefully dividing the ligamentum arteriosum and attached connective tissue. An 18-mm flow transducer (Statham SP7516–019) was applied to the pulmonary artery and in all animals a close fit was obtained. The two flow transducers were connected to flow meters with a non-occlusive zero facility (Statham SP2202). Thus flow could be measured simultaneously in a major coronary artery and in the pulmonary artery (cardiac output). In four of the animals a rigid catheter (Cournand type) was inserted into the left ventricle via the left common carotid artery for measurement of the maximum rate of increase of left ventricular pressure (l.v. d*p*/d*t* max). The Cournand catheter was connected to an Elema–Schonander transducer (EMT 34), the signal from which was differentiated electronically to give d*p*/d*t* max. The frequency response of this system was assessed *in*

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vitro and found to be satisfactory up to 25 Hz. During the measurement of d*p*/d*t* max, frequencies in excess of 20 Hz were filtered electronically. Positive end-expiratory pressure (PEEP) of 5 cm H_2O was applied to the expiratory limb of the ventilator tubing to minimize pulmonary collapse and the exposed thoracic tissues were kept moist with swabs soaked in physiological saline.

The blood-gas tensions and pH were measured with suitably calibrated electrodes (Instrumentation Laboratories, I.L. 182) and corrected for any temperature difference between the animal's mid-oesophagus and the electrode. The haemoglobin concentration was measured using a co-oximeter (Instrumentation Laboratories, I.L. 213). Arterial hypotension was produced by the infusion of a 0.01% solution of sodium nitroprusside in physiological saline into a fore-leg vein. In each animal the arterial pressure was decreased to four different values—100–90 mm Hg, 90–80 mm Hg, 80–70 mm Hg and 70–60 mm Hg. The rate of infusion necessary to attain the required hypotension varied according to the sensitivity of the animal to nitroprusside, the range being 0.5–1.6 ml min^{-1} (0.05–0.16 mg min^{-1}). These infusion rates were slowed appropriately when the desired hypotension was achieved. The mean duration of infusion was 11 min and the mean duration of stable hypotension was 7.2 min. The arterial pressure was allowed to return to its control value between each period of hypotension and the order in which the various levels of hypotension were attained was randomized. On cessation of the infusion, all values returned to control values within 4 min except for the heart rate, which took up to 10 min to return to control.

Blood oxygen saturation was calculated from Po_2, taking into account pH and temperature. Blood oxygen content was then calculated as follows:

$$\text{O}_2 \text{ content (ml dl}^{-1}) = \text{Hb (g dl}^{-1}) \times 1.36 \times \frac{\%\ \text{saturation}}{100} + Po_2\ (\text{kPa}) \times 0.0232$$

This method of oxygen content calculation as used in this laboratory has been shown to correlate satisfactorily with the direct method of Van-Slyke (Ledingham et al., 1971).

The following data were derived:

Myocardial O_2 consumption (ml min^{-1})

$$= (Ca_{O_2} - Ccs_{O_2})\ (\text{ml dl}^{-1}) \times \text{coronary flow (ml min}^{-1}) \times 1/100$$

Total body O_2 consumption (ml min^{-1})

$$= (Ca_{O_2} - C\bar{v}_{O_2})\ (\text{ml dl}^{-1}) \times \text{CO (litre min}^{-1}) \times 10$$

Myocardial O_2 extraction (%)

$$= \frac{(Ca_{O_2} - Ccs_{O_2})\ (\text{ml dl}^{-1})}{Ca_{O_2}\ (\text{ml dl}^{-1})} \times \frac{100}{1}$$

Total O_2 extraction (%)

$$= \frac{(Ca_{O_2} - C\bar{v}_{O_2})\ (\text{ml dl}^{-1})}{Ca_{O_2}\ (\text{ml dl}^{-1})} \times \frac{100}{1}$$

Coronary artery resistance (units) =

$$\frac{\text{arterial pressure} - \text{right atrial pressure (mm Hg)}}{\text{coronary flow (ml min}^{-1})} \times \frac{10}{1}$$

Total peripheral resistance (units) =

$$\frac{\text{arterial pressure} - \text{right atrial pressure (mm Hg)}}{\text{CO (litre min}^{-1})} \times \frac{10}{1}$$

where Ca_{O_2} = arterial oxygen content; Ccs_{O_2} = coronary sinus oxygen content; $C\bar{v}_{O_2}$ = mixed venous oxygen content; CO = cardiac output.

It is assumed for the above calculations that coronary sinus blood was representative of the venous effluent of the area perfused by the artery whose flow was measured and that right atrial blood may be regarded as mixed venous.

In order to confirm the accuracy of the flow measuring system, in one animal a branch of the left femoral artery of appropriate size was dissected out. A cannula was inserted into the vessel which was then ligated distally and the 2.0-mm flow transducer attached proximally with a gate clamp still more proximally. The blood from the vessel was drained through the cannula into a graduated measuring cylinder over timed periods of 0.5 or 1 min. Absolute flow could thus be compared with mean flow measured by the meter and the flow rate varied by means of the gate clamp.

The changes produced during each hypotensive period were compared with the control values obtained immediately before. Comparisons were made using a Student's *t* test for paired data and the *P* values are stated where significant changes took place ($P < 0.05$).

RESULTS

The comparison between the flows measured by collection over timed periods and the flows measured by the meter are presented in figure 1. A satisfactory correlation was demonstrated ($r = 0.99$, $y = 1.134x - 9.00$).

The initial response noted on the infusion of nitroprusside solution was a small but consistent increase in mean coronary arterial blood flow which returned to its control value as the arterial pressure decreased.

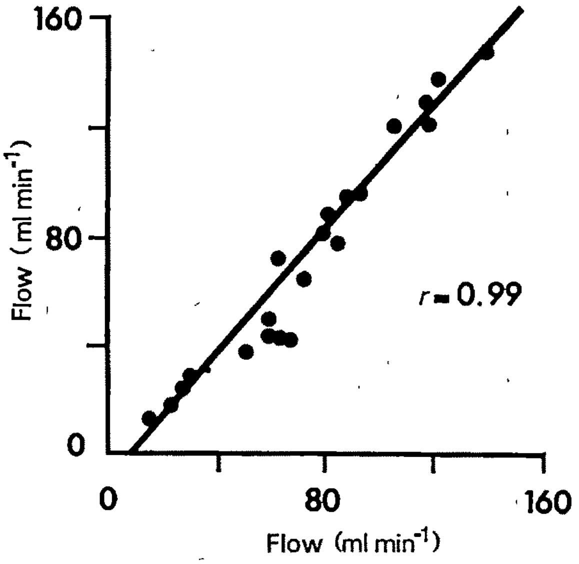

FIG. 1. Comparison of measured flow using the flow meter (x axis) and the measured flow by collection using a measuring cylinder (y axis).

Subsequently, the most striking feature was that, despite an average decrease in mean arterial pressure of up to about 50%, the mean coronary artery flow and the cardiac output were not altered significantly (table I). Coronary artery resistance and total peripheral resistance both decreased progressively as the arterial pressure decreased and they did so in a manner which was similar in magnitude. There was a significant increase in heart rate during each period of hypotension and this became proportionately higher as the arterial pressure became less.

Myocardial oxygen consumption did not change significantly and as the blood flow was unchanged the oxygen extraction by the myocardium was unchanged also. Similar comments apply to total body oxygen consumption and extraction.

Table II shows the changes which occurred in dp/dt max in four individual dogs. There was a consistent reduction in dp/dt max during all levels of hypotension and the reduction was progressively greater as the decrease in arterial pressure became greater.

Apart from the increase in heart rate, no animal showed any electrocardiographic changes during the periods of hypotension.

TABLE I. *Changes in haemodynamic variables and oxygen consumption at four levels of hypotension produced by infusion of a* 0.01% *solution of sodium nitroprusside (seven dogs, mean* ± *SEM)*

	Control	Hypotension	Control	Hypotension	Control	Hypotension	Control	Hypotension
Mean aortic pressure (mm Hg)	122±2	92±0.9	126±3	83±1	124±4	72±0.9	121±2.5	62.3±1.2
Heart rate (beat min^{-1})	189±11	236±16	198±16	227±9	179±15	227±16	179±16	221±19
	($P<0.01$)		($P<0.025$)		($P<0.001$)		($P<0.001$)	
Mean coronary artery flow (ml min^{-1})	55±14	53±9	46±6	47±7	48±6	42±7	43±6	40±6
Coronary artery resistance (units)	27.1±3.0	20.3±3.2	28.8±2.8	20.4±3.3	28.2±3.6	19.4±3.1	30.2±3.1	15.9±2.0
	($P<0.05$)		($P<0.01$)		($P<0.01$)		($P<0.0025$)	
Cardiac output (litre min^{-1})	5.11±0.46	5.24±0.35	5.2±0.4	4.9±0.3	5.18±0.29	4.8±0.28	5.16±0.28	5.11±0.26
Total peripheral resistance (units)	246±21	177±13	240±21	170±13	241±19	146±9	233±12	118±10
	($P<0.005$)		($P<0.005$)		($P<0.001$)		($P<0.001$)	
Myocardial O_2 consumption (ml min^{-1})	4.0±1.7	3.8±0.7	4.1±0.8	3.9±0.6	4.2±0.5	3.9±0.5	3.9±0.7	3.7±0.5
Myocardial O_2 extraction (%)	35.1±4	32.3±4	35.4±3	32.3±3	34.7±3	32±3	30.7±3	28.7±4
Total O_2 consumption (ml min^{-1})	164±25	156±27	178±23	160±20	145±19	159±19	156±15	164±24
Total O_2 extraction (%)	14.1±2	12.2±2	13.7±2	13.0±1	11.2±1	12.8±1	12.1±1	14.1±2

TABLE II. *Changes in dp/dt max (mm Hg s^{-1}) in four individual dogs during periods of hypotension produced by the infusion of sodium nitroprusside*

	Mean arterial pressure (mm Hg)									
Dog	Control	100–90	Control	90–80	Control	80–70	Control	70–60	Control	60–50
1	2300	2000	2400	2000	2400	1800	2200	1600	2300	1600
2	2400	1900	2400	1900	2500	1700	2500	1400	2300	1000
3	2400	2000	2500	2000	2300	1900	2100	2000	—	—
4	3300	3000	3400	2800	3400	2200	3000	2000	3200	1800

DISCUSSION

Sodium nitroprusside has been used to produce deliberate hypotension as an adjunct to anaesthesia in many circumstances, as for example in neurosurgery (Siegel, Moraca and Green, 1971), major e.n.t. surgery (Wildsmith, Drummond and MacRae, 1975) and major orthopaedic surgery (Simpson, Bellamy and Cole, 1976). It produces hypotension by a direct vasodilator effect on the blood vessels themselves. As with every technique of hypotensive anaesthesia, there is concern about perfusion of vital tissues and several workers have attempted to assess the adequacy of myocardial oxygenation during hypotension produced by nitroprusside. Simpson, Bellamy and Cole (1976), using the rather crude method of electrocardiography, concluded that none of their patients suffered permanent myocardial ischaemia although some did show minor but transient changes in the ST-segments and T-waves. A study by Ross and Cole (1973) suggested that in four dogs anaesthetized with chloralose, coronary flow and cardiac output increased during hypotension induced with nitroprusside while Wang, Liu and Katz (1977) observed that nitroprusside decreased coronary flow. Increases in cardiac output have been recorded also during the infusion of nitroprusside on a background of nitrous oxide and halothane anaesthesia (Wildsmith et al., 1973).

The present study has shown that in the dog anaesthetized with a barbiturate, the i.v. infusion of sodium nitroprusside caused a transient and small increase in coronary blood flow which returned to control values as the animal became progressively hypotensive. Thereafter, the coronary flow did not alter significantly. This initial small increase in flow reflects probably the fact that the coronary arteries are the first to receive the drug and thus react to it before it affects the peripheral vasculature. Cardiac output showed no significant changes during the periods of hypotension. In those dogs in which it was measured there were consistent decreases in left ventricular d*p*/d*t* max, suggesting that myocardial contractility had decreased. Increases in the heart rate during the infusion of nitroprusside were a consistent feature and probably contributed to the maintenance of cardiac output and of myocardial oxygen extraction and consumption. Otherwise these latter might have been expected to decrease as the after-load of the heart was reduced during the periods of hypotension. There were marked decreases in both myocardial and total peripheral vascular resistances during hypotension and indeed this is the means by which nitroprusside produces its hypotensive action.

Studies of the influence of nitroprusside on cardiac output have shown varying results. In patients with myocardial infarction, in whom there was left ventricular failure and a low cardiac index, Franciosa and others (1972) described an increase of cardiac output with an infusion of nitroprusside. However, in those patients in whom the cardiac index was normal after infarction, nitroprusside produced no change in cardiac output. A complex study by Adams and others (1974) in dogs anaesthetized with nitrous oxide and halothane suggested that cardiac output was unchanged during the infusion of nitroprusside and that left ventricular d*p*/d*t* max was reduced in a dose-dependent manner. Our study is in agreement with these latter findings.

This study showed that during hypotension induced with nitroprusside, the coronary flow was well maintained. This is in contrast to the situation in which hypotension was induced with halothane when coronary vasoconstriction occurred (Smith et al., 1974). Therefore, these findings would suggest that hypotension brought about by nitroprusside is inherently safer as regards myocardial perfusion. The fact that a major degree of coronary vasodilatation occurred during hypotension indicates that, at least at the lower values of arterial pressure, there may be little capacity for further vasodilatation, for example in response to haemorrhage. The importance of maintaining blood volume during induced hypotension must be stressed.

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EFFET DE L'HYPOTENSION PROVOQUEE PAR LE NITROPRUSSIATE DE SODIUM SUR LE DEBIT DE L'ARTERE CORONAIRE DES CHIENS

RESUME

On a mesuré le débit sanguin de l'artère pulmonaire et de l'artère coronaire de sept chiens anesthésiés au pentobarbitone, en employant des débitmètres électromagnétiques. L'infusion d'une solution de nitroprussiate de sodium à 0,01% a provoqué une légère augmentation initiale du débit moyen de l'artère coronaire, lequel est retourné aux valeurs témoins au fur et à mesure que la pression artérielle a diminué. On n'à remarqué aucune variation dans le débit cardiaque et on n'a observé aucun autre changement dans le débit coronaire. La fréquence cardiaque a augmenté d'une manière continue pendant l'hypotension et la dp/dt maximale ventriculaire gauche a diminué tout comme les résistances périphériques totale et coronaire. Il n'y a eu aucune variation importante dans la consommation ou l'extraction de l'oxygène du corps ou du myocarde.

DER EINFLUSS VON DURCH NITROPRUSSIDNATRIUM HERBEIGEFÜHRTER HYPOTONIE AUF DEN HERZKRANZARTERIENFLUSS IN HUNDEN

ZUSAMMENFASSUNG

In sieben mit Pentobarbiton anästhesierten Hunden wurden die Herzkranz- und Lungenarterienflusse unter Verwendung von elektromagnetischen Stromungsmessern gemessen Die Infusion einer 0,01-prozentigen Lösung von Nitroprussidnatrium verursachte eine anfängliche geringfügige Erhöhung des mittleren Herzkranzarterienflusses, der mit Abfall des arteriellen Drucks auf den Bezugspegel zuruckfiel. Im Herzminutenvolum wurden keine Veränderungen festgestellt, noch wurden weitere Veränderungen im Herzkranzfluss beobachtet. Während der Hypotonie war die Pulszahl anhaltend erhöht und der linksventrikuläre dp/dt max sowie der Herzkranz- und periphere Gesamtwiderstand waren niedriger. In der Sauerstoffausscheidung oder im Sauerstoffverbrauch des Herzmuskels bzw. des gesamten Korpers fanden keine bedeutsamen Veränderungen statt.

EFECTO EJERCIDO POR HIPOTENSION INDUCIDA POR NITROPRUSIATO SODICO SOBRE LA CIRCULACION ARTERIAL CORONARIA CANINA

SUMARIO

Se midieron las circulaciones de sangre arterial pulmonar y coronaria en siete perros anestesiados con pentobarbitona, empleando para tal fin flujómetros electromagnéticos. La infusión de una solución con 0,01% de nitroprusiato sódico provocó un pequeño aumento inicial en la circulación arterial coronaria media, que volvió a su valor de control a medida que disminuyó la presión arterial. No se notaron cambios en la capacidad cardíaca ni se observaron cambios adicionales en la circulación coronaria. Los latidos del corazón aumentaron consistentemente durante la hipotensión y se redujo el dp/dt max ventricular izquierdo, así como las resistencias coronaria y periférica total. No se produjeron cambios significativos en la extracción ni consumo del oxígeno miocardíaco ni total del cuerpo.

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DEPRESSION OF HYPOXIC PULMONARY VASOCONSTRICTION IN THE DOG BY DOPAMINE AND ISOPRENALINE

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SUMMARY

The effects of dopamine and isoprenaline on the pulmonary vasoconstrictor response to alveolar hypoxia were assessed by measuring the redistribution of blood flow between the lungs in response to unilateral hypoxia. Dose rates of dopamine 25 $\mu g\ kg^{-1}\ min^{-1}$ and isoprenaline 0.25 $\mu g\ kg^{-1}\ min^{-1}$ (which produced equal increments in the contractile force of the heart in dogs) produced a similar degree of depression of the hypoxic vasoconstrictor response, whereas dopamine 2.5 $\mu g\ kg^{-1}\ min^{-1}$ had little effect on the response. Pa_{O_2} during unilateral hypoxia was inversely related to the blood flow through the hypoxic lung.

The i.v. infusion of isoprenaline or dopamine to patients with cardiorespiratory disease may result in a marked decrease in Pa_{O_2} (Fordham and Resnekov, 1968; Mulroy and Fairley, 1977; Rapin et al., 1977) for which there are several possible explanations. First the drug may stimulate tissue oxygen demand more than cardiac output so that the mixed venous oxygen tension decreases. As a result, the Po_2 of the blood passing through non-ventilated areas of lung would decrease, thus decreasing Pa_{O_2}. A second explanation is that the drug may open up anastomotic pathways, which are closed normally, between the right and left sides of the lung either by a direct effect on the anastomotic vessels or by increasing the pulmonary artery pressure (Tobin, 1966). A third possibility is that the drug may increase ventilation/perfusion inequality by altering the distribution of ventilation or perfusion. A redistribution of perfusion to poorly ventilated parts of the lung could be produced by an alteration in pulmonary vascular pressures secondary to a change in cardiac output, by a direct dilator or constrictor action of the drug on the pulmonary blood vessels or by depression of the hypoxic pulmonary vasoconstrictor mechanism which normally diverts blood flow away from areas of lung with a low alveolar Po_2 (Hughes, 1975).

The present experiments were designed to elucidate whether the i.v. infusion of dopamine produced a dose-dependent depression of the pulmonary vasoconstrictor response to alveolar hypoxia and whether those dose rates of isoprenaline and dopamine which produced equal increases in myocardial contractile force in the dog produced a similar degree of depression of the hypoxic response. It had been found in a previous series of experiments that a dose rate of dopamine 25 $\mu g\ kg^{-1}\ min^{-1}$ produced the same increase in contractile force as isoprenaline 0.25 $\mu g\ kg^{-1}\ min^{-1}$ (Marin-Neto and colleagues, in preparation). These doses were compared with a dose rate of dopamine 2.5 $\mu g\ kg^{-1}\ min^{-1}$ to ascertain whether the effect on the hypoxic vasoconstrictor response was dose-dependent. The response was assessed at each stage of the experiment by measuring the redistribution of pulmonary blood flow between the two lungs in response to unilateral alveolar hypoxia produced by ventilating the left lung with oxygen 7% in nitrogen.

METHODS

The experiments were performed on eight dogs of various breeds weighing 18–30 kg. They were anaesthetized with thiopentone 20–30 $mg\ kg^{-1}$ i.v. followed by pentobarbitone 60–180 mg, additional small doses of thiopentone being given throughout the experiment when required.

The animals were placed supine in a V-shaped trough and the trachea was intubated with a cuffed tube. Ventilation of the lungs was controlled with a Cape ventilator adjusted to provide an end-tidal carbon dioxide concentration of 4–5%, at a constant frequency of 15 b.p.m.

The right and left femoral vessels were cannulated to allow measurement of cardiac output by dye

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dilution, blood sampling, direct arterial pressure measurement and the continuous infusion of xenon-133 solution into the inferior vena cava. Swan–Ganz and polyethylene catheters were floated into the pulmonary artery for the recording of pulmonary artery and wedge pressures (Fife and Lee, 1965; Swan et al., 1970; Lozman et al., 1974). All the pressures were recorded with Consolidated Electrodynamics strain gauges and displayed on a Devices M19 heated stylus recorder, the transducers being calibrated repeatedly against a saline column.

Blood flow, cardiac output and blood-gas measurement

The techniques used for these measurements have been described previously (Sykes, Hurtig et al., 1977 a, b). A tracheal divider (Seed and Sykes, 1972) was inserted and the ventilation to each lung controlled at constant tidal volume by two second-stage ventilator systems which permitted the gas concentrations to each lung to be varied independently. The distribution of blood flow between the two lungs was measured continuously by recording the radioactivity of the mixed expired gas from each lung whilst xenon-133 solution was infused continuously into the inferior vena cava. Since the quantity of xenon delivered to each lung is proportional to its blood flow, and since approximately 95% of the gas is evolved during its first passage through the lungs, there is a direct relationship between the ratio of the mixed expired activity from each lung and the ratio of blood flows. The technique has been evaluated and shown to be sufficiently accurate for this work (Sykes, Hill et al., 1977). Cardiac output measurements were made by the dye dilution technique using indocyanine green dye whilst measurements of blood-gas tensions and pH were made on duplicate electrode systems at 37 °C and corrected to body temperature (Sykes et al., 1970). Haemoglobin was determined by the cyanmethaemoglobin method.

Experimental programme

Both lungs were ventilated initially with oxygen 100% and the ventilation to each lung was adjusted to produce an end-tidal carbon dioxide concentration of 4–5% with equal counts of radioactivity on each side. Since the counting geometry was matched carefully this indicated that ventilation was evenly matched to blood flow.

After 30 min to allow stabilization, mean arterial, pulmonary artery and wedge pressures were recorded, together with duplicate dye dilution curves. Pulmonary artery and systemic arterial samples were drawn for measurement of blood-gas tensions, pH and Hb concentration. The end-tidal carbon dioxide concentrations and airway pressures were recorded also.

The hypoxic response was then tested by ventilating the left lung with oxygen 7% in nitrogen whilst the right lung was still ventilated with oxygen. The diversion of blood flow from the hypoxic to the oxygenated lung was followed on the recorder and, at about 10 min, when the diversion had reached its peak, a full set of measurements was repeated. Bilateral ventilation with oxygen was resumed and an i.v. infusion of dopamine 2.5 $\mu g\ kg^{-1}\ min^{-1}$ started. Another set of measurements was made 10 min after starting the infusion and the left lung then ventilated with oxygen 7% in nitrogen. The fourth set of measurements was made at the peak of the diversion, the infusion turned off and bilateral ventilation with oxygen resumed. Thirty minutes later measurements were made on bilateral oxygen and again at the peak of the second control hypoxic response. The sequence of measurements on oxygen and oxygen 7% was repeated during the infusion of dopamine 25 $\mu g\ kg^{-1}\ min^{-1}$ and during the infusion of isoprenaline 0.25 $\mu g\ kg^{-1}\ min^{-1}$.

In these experiments the hypoxic stimulus was always applied to the left lung so that it proved convenient to express the distribution of blood flow in terms of the peak right-to-left ratio of xenon-133 counts. These were determined by visual averaging of the tracing. Thus when ventilation was matched correctly to blood flow on bilateral oxygen the ratio was 1, but when unilateral hypoxia to the left lung caused a diversion of blood flow away from that lung the ratio was increased.

Since R/L ratios of blood flow are not distributed normally, statistical analysis was performed by Wilcoxon's signed rank test. The remainder of the data was subjected to a two-way analysis of variance.

RESULTS

Blood flow measurements

A typical record of a hypoxic response obtained before, during and after the administration of dopamine 25 $\mu g\ kg^{-1}\ min^{-1}$ is presented in figure 1. Table I shows the individual measurements of R/L ratios of blood flow at each stage of the experiment, the meaned results being illustrated in figure 2. The R/L ratios during unilateral hypoxia were usually smaller during the initial control period (C_1) than during the three subsequent control periods (C_2, C_3 and C_4) although the differences only reached

TABLE I. *Changes in R/L ratio in response to unilateral hypoxia in eight dogs before, during and after the administration of dopamine 2.5 μg kg^{-1} min^{-1}, dopamine 25 μg kg^{-1} mnn^{-1} and isoprenaline 0.25 μg kg^{-1} min^{-1}*

	Control 1		Dopamine 2.5 μg kg^{-1} min^{-1}		Control 2		Dopamine 25 μg kg^{-1} min^{-1}		Control 3		Isoprenaline 0.25 μg kg^{-1} min^{-1}		Control 4	
	A	B	C	D	E	F	G	H	I	J	K	L	M	N
Dog no.	O_2/O_2	$O_2/7\%$	O_2/O_2	$O_2/7\%$	O_2/O_2	$O_2/7\%$	O_2/O_2	$O_2/7\%$	O_2/O_2	$O_2/7\%$	O_2/O_2	$O_2/7\%$	O_2/O_2	$O_2/7\%$
1	1.0	2.06	1.04	3.1	1.0	3.3	1.0	1.43	1.0	5.3	1.0	1.37	1.0	4.64
2	1.0	1.43	1.0	1.56	1.0	3.75	1.0	1.29	1.0	3.13	1.14	1.43	1.0	2.80
3	1.0	1.32	1.01	1.86	1.0	2.1	1.0	1.1	1.0	2.28	1.0	1.21	1.08	2.0
4	1.0	1.70	1.0	1.73	1.0	1.88	1.0	1.1	1.0	1.65	1.0	1.10	1.0	1.77
5	1.0	1.76	1.0	1.66	1.0	1.85	1.0	1.04	1.04	2.8	1.0	1.44	1.0	2.95
6	1.0	1.8	1.0	1.25	1.0	1.22	1.0	1.1	1.1	1.5	1.0	1.04	1.1	2.0
7	1 0	1.45	1.0	1.67	1.0	1.78	1.1	1.35	1.0	1.95	1.0	1.50	1.1	2.06
8	1.0	2.30	1.0	1.58	1.0	2.0	1.0	1.0	1.0	2.03	1.0	1.00	1.0	2.08
Mean	1.0	1.73	1.01	1.80	1.0	2.24	1.01	1.18	1.01	2.58	1.02	1.26	1.04	2.54
Statistical comparisons				F*				D** F** J**				D** J** N**	A*	B**

* $P < 0.05$; ** $P < 0.01$.

TABLE II. *Cardiovascular measurements, airway pressure and end-tidal carbon dioxide concentration at each stage of the experiment (mean ± SD). For symbols see text. The letters in the table indicate the statistical comparisons in which the P values were* < 0.05

		Control 1		Dopamine 2.5 µg kg^{-1} min^{-1}		Control 2		Dopamine 25 µg kg^{-1} min^{-1}		Control 3		Isoprenaline 0.25 µg kg^{-1} min^{-1}		Control 4	
		A	B	C	D	E	F	G	H	I	J	K	L	M	N
		O_2/O_2	$O_2/7\%$	O_2/O_2	$O_2/7\%$	O_2/O_2	$O_2/7\%$	O_2/O_2	$O_2/7\%$	O_2/O_2	$O_2/7\%$	O_2/O_2	$O_2/7\%$	O_2/O_2	$O_2/7\%$
$P_{\overline{AO}}$ (mm Hg)		147.5 ±20.8	146.8 ±13.8	A, E 166.9 ±9.6	B, F 165.6 ±10.8	154.4 ±18.6	150.6 ±15.9	E, I 183.8 ±16.9	F, J 195.6 ±14.2	130.6 ±15.2	134.4 ±16.3	I, M 100.1 ±7.6	J, N 111.9 ±12.3	A 125.6 ±14.2	B 125.6 ±12.9
$P_{\overline{PA}}$ (mm Hg)		11.9 ±1.7	A 12.8 ±1.8	12.3 ±2.1	B, C 14.4 ±1.97	11.9 ±1.93	B, E 14.8 ±1.46	E 15.9 ±3.59	F, G 17.2 ±3.3	14.9 ±3.16	I, B 16.9 ±3.04	I, L 15.4 ±3.30	K 17.4 ±3.81	A 16.3 ±4.40	B, L 16.6 ±3.73
$P_{\overline{LA}}$ (mm Hg)		4.6 ±2.3	3.9 ±1.6	4.9 ±2.5	4.7 ±2.0	4.6 ±2.2	5.2 ±1.7	E 5.8 ±2.3	5.0 ±2.3	5.9 ±2.2	H 5.7 ±2.6	5.5 ±3.2	5.7 ±3.3	5.7 ±2.3	5.8 ±2.1
$\dot{Q}$ (litre min^{-1})		2.6 ±0.25	2.4 ±0.48	2.4 ±0.61	2.3 ±0.55	A 1.8 ±0.51	B 1.9 ±0.44	E 2.4 ±0.9	F 2.6 ±0.51	2.1 ±0.41	H 1.8 ±0.31	I, M 3.2 ±0.86	J, N 3.4 ±0.9	2.8 ±0.58	2.4 ±0.42
PVR (mm Hg $litre^{-1}$ min^{-1})		3.16 ±1.07	A 4.21 ±1.28	D, E 3.23 ±0.74	4.29 ±0.75	C 4.28 ±1.44	E, D 5.34 ±1.38	4.50 ±1.37	J 4.88 ±0.91	4.79 ±2.05	I, B, F 6.48 ±1.9	4.14 ±1.31	J, N 4.09 ±2.12	I 3.99 ±2.0	B, D 5.08 ±2.38
Airway pressure (cm H_2O)	R	9.2 ±1.5	9.2 ±1.3	9.5 ±1.2	9.7 ±1.1	10.1 ±1.3	10.1 ±1.2	10.3 ±1.2	10.1 ±1.0	10.2 ±1.2	10.2 ±1.2	9.9 ±1.4	9.9 ±1.4	10.0 ±1.3	10.3 ±1.2
	L	9.8 ±1.7	10.3 ±1.6	10.5 ±1.6	B 11.0 ±1.6	10.7 ±1.5	B 11.4 ±1.4	11.3 ±1.6	11.5 ±1.8	11.3 ±1.6	B 11.5 ±1.4	10.5 ±1.7	11.0 ±1.4	11.0 ±1.4	B 11.3 ±1.5
$ETco_2$(%)	R	B 4.7 ±0.38	5.2 ±0.49	D 4.6 ±0.32	5.0 ±0.41	F 4.5 ±0.29	4.9 ±0.61	H 4.9 ±0.52	5.6 ±0.59	J 4.7 ±0.60	5.3 ±0.76	L 5.5 ±0.79	J 6.0 ±0.97	N 5.4 ±1.0	5.7 ±1.1
	L	B 4.7 ±0.50	4.3 ±0.46	D 4.6 ±0.37	3.9 ±0.42	F 4.4 ±0.30	3.7 ±0.46	4.9 ±0.56	5.0 ±0.96	J 4.6 ±0.58	3.6 ±0.47	5.4 ±0.82	J, N 5.3 ±0.83	N 5.3 ±1.0	3.7 ±0.68

TABLE III. *Blood-gas tensions, hydrogen ion concentration, base excess and haemoglobin concentration at each stage of the experiment (mean ± SD). For symbols see text. The letters in the table indicate the statistical comparisons in which $P < 0.05$*

	Control 1		Dopamine 2.5 µg kg⁻¹ min⁻¹		Control 2		Dopamine 25 µg kg⁻¹ min⁻¹		Control 3		Isoprenaline 0.25 µg kg⁻¹ min⁻¹		Control 4	
	A	B	C	D	E	F	G	H	I	J	K	L	M	N
	O_2/O_2	$O_2/7\%$	O_2/O_2	$O_2/7\%$	O_2/O_2	$O_2/7\%$	O_2/O_2	$O_2/7\%$	O_2/O_2	$O_2/7\%$	O_2/O_2	$O_2/7\%$	O_2/O_2	$O_2/7\%$
Pa_{O_2} (kPa)	B 59.5 ±3.2	26.6 ±1.17	D 58.8 ±6.8	25.4 ±0.99	F 58.7 ±5.5	27.0 ±0.84	H 57.1 ±5.8	F, J 16.5 ±0.57	J 57.5 ±7.1	28.2 ±0.6	L 55.6 ±9.2	J, N 18.0 ±0.51	N 56.0 ±6.0	28.9 ±1.1
$P\bar{v}_{O_2}$ (kPa)	B 8.2 ±1.32	7.0 ±0.84	D 7.9 ±0.99	7.0 ±0.35	F 7.9 ±1.24	6.9 ±0.76	E, I 8.4 ±1.19	6.9 ±0.75	7.3 ±0.34	7.0 ±0.76	I, M 8.8 ±0.97	J, N 7.6 ±1.54	N 7.8 ±1.15	L 6.9 ±1.18
Pa_{CO_2} (kPa)	5.2 ±0.25	5.3 ±0.55	5.1 ±0.53	5.2 ±0.56	5.1 ±0.51	5.2 ±0.41	E, I 5.6 ±0.35	F, J 5.8 ±0.38	5.2 ±0.34	5.3 ±0.47	5.7 ±0.70	J, N 6.3 ±0.72	5.7 ±0.49	5.8 ±0.56
[illegible]	[illegible] ±0.37	[illegible] ±0.64	[illegible] ±0.58	[illegible] ±0.65	[illegible] ±0.68	[illegible] ±0.53	H [illegible] ±0.40	F, J [illegible] ±0.97	[illegible] ±0.62	[illegible] ±0.71	I [illegible] ±1.0	J [illegible] ±0.86	[illegible] ±1.07	J [illegible] ±0.66
BE (mmol litre⁻¹)	−(3.4 ±1.2)	−(3.8 ±0.6)	−(3.5 ±1.8)	−(3.6 ±1.1)	−(3.6 ±1.5)	−(3.4 ±1.3)	E, I −(5.0 ±1.9)	F, J −(7.5 ±2.2)	−(6.5 ±1.5)	−(5.5 ±1.7)	−(6.4 ±2.1)	J, N −(8.2 ±1.6)	A −(6.8 ±2.3)	B −(6.1 ±1.3)
[H⁺] (nmol litre⁻¹)	44	45	44	44	44	45	E,C,A 50	F,J,B,D 57	G 51	H 51	I 55	J, N 61	A 55	J, B, L 54
Hb (g dl⁻¹)	14.4 ±1.8	14.5 ±2.3	14.4 ±2.1	14.4 ±2.1	14.3 ±2.0	14.2 ±1.9	14.6 ±2.0	15.2 ±2.2	14.5 ±2.3	13.9 ±2.1	13.8 ±2.1	13.6 ±2.1	13.3 ±1.7	13.2 ±1.8

statistical significance when C_4 was compared with C_1. The R/L ratios on unilateral hypoxia during the administration of the low dose of dopamine were not significantly different from the ratios during unilateral hypoxia at C_1 but were significantly less than the ratios on hypoxia at C_2. During the administration of the high dose of dopamine and during the administration of isoprenaline the ratios during unilateral hypoxia were significantly less than those obtained during the control periods before and after the administration of the drugs. The response to hypoxia during the administration of the high dose of dopamine was significantly less than the response during the administration of the low dose.

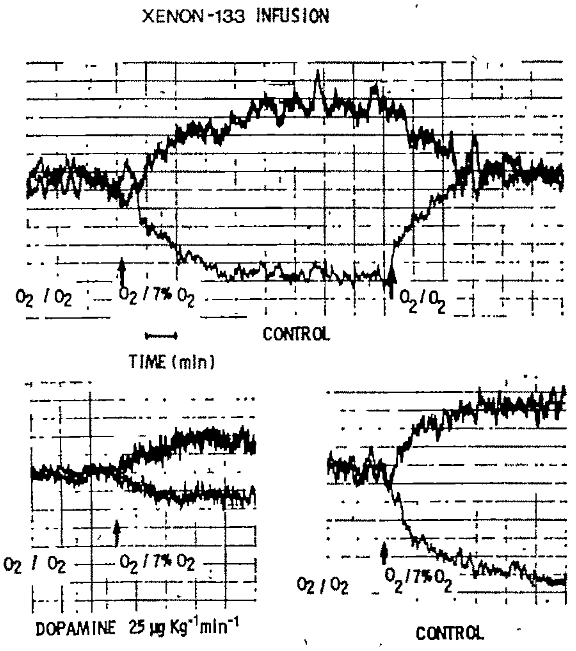

FIG. 1. Typical records of the radioactivity of mixed expired gas from each lung (ordinate) before, during and after the administration of dopamine 25 µg kg^{-1} min^{-1}. Time along the abscissa. When the left lung is made hypoxic by the administration of oxygen 7% in nitrogen there is a reduction in radioactivity of gas from the hypoxic lung and an increase in count rate from the oxygenated lung. The redistribution of blood flow in response to unilateral hypoxia is depressed during the infusion of dopamine, but the response returns when the drug is withdrawn.

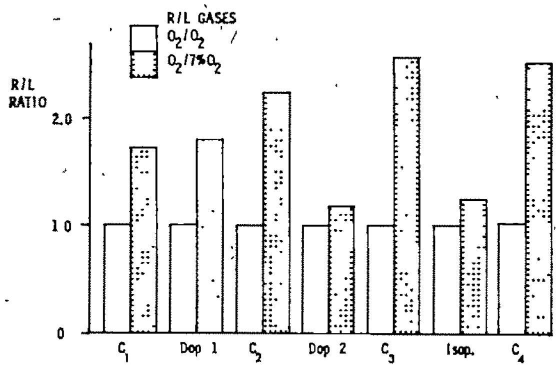

FIG. 2. Mean right-to-left (R/L) ratios of blood flow throughout the experiment. The response to the unilateral administration of oxygen 7% in nitrogen was tested in the control periods when no drug was being given (C_1, C_2, C_3 and C_4), during the administration of dopamine 2.5 and 25 µg kg^{-1} min^{-1} (Dop. 1 and Dop. 2) and during the administration of isoprenaline 0.25 µg kg^{-1} min^{-1} (Isop.). Significant depression of the response occurred with the high dose of dopamine and with isoprenaline.

Cardiovascular and respiratory measurements (Tables II, III).

Changes produced by dopamine and isoprenaline on bilateral oxygen. There was a significant increase in mean aortic pressure ($P_{\overline{AO}}$) during the administration of both doses of dopamine and a significant decrease during the administration of isoprenaline. Mean pulmonary artery pressure ($P_{\overline{PA}}$) increased significantly both with the high dose of dopamine and with isoprenaline, whilst mean pulmonary artery wedge pressure ($P_{\overline{LA}}$) increased significantly only in response to the high dose of dopamine. Cardiac output ($\dot{Q}$) decreased after the initial dose of dopamine but was significantly greater during the high dose of dopamine than during C_2. During isoprenaline infusion $\dot{Q}$ was significantly greater than during C_3 or C_4. Mixed venous oxygen tension ($P\bar{v}_{O_2}$) and Pa_{CO_2} were significantly greater during the administration of the high dose of dopamine and during isoprenaline infusion than during the control periods before and after administration of the drugs. Both the high dose of dopamine and the isoprenaline infusion produced a reduction in the calculated base excess (BE) so that hydrogen ion concentration [H$^+$] was significantly greater at the end of the experiment than at the beginning.

Responses to unilateral hypoxia. There were no significant changes in Pa_{O_2} on bilateral oxygen throughout the experiment, but there were significant reductions in Pa_{O} when the left lung was ventilated with oxygen 7%. The changes in Pa_{O_2} in response to hypoxia mirrored the changes in blood flow. Thus Pa_{O_2} during the administration of the low dose of dopamine was not significantly different from that measured during unilateral hypoxia at C_1 and C_2, but Pa_{O_2} during the administration of both the high dose of dopamine and isoprenaline was significantly less than Pa_{O_2} during unilateral hypoxia in the control periods before and after drug infusion (fig. 3).

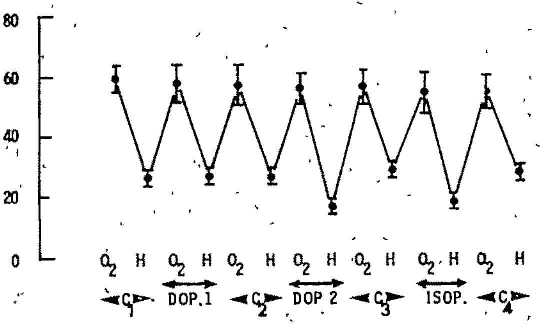

FIG. 3. Arterial Po_2 values (mean ± SD) during bilateral administration of oxygen (above) and during unilateral hypoxia (below). The reduction in Pa_{O_2} in response to unilateral hypoxia was significantly greater during the infusions of the high dose of dopamine and isoprenaline than during the control periods before or after (C_2, C_3, C_4).

There were small increases in airway pressure on the left side in response to the administration of the hypoxic gas mixture whilst the alterations in end-tidal carbon dioxide concentrations ($ETco_2$) closely paralleled the changes observed in the distribution of pulmonary blood flow.

DISCUSSION

These experiments showed that the 25-μg kg^{-1} min^{-1} dose rate of dopamine and the 0.25-μg kg^{-1} min^{-1} dose rate of isoprenaline produced a similar depression of the pulmonary vasoconstrictor response to unilateral hypoxia whilst the low dose of dopamine had little effect. These observations were confirmed by the observation that arterial Po_2 during unilateral hypoxia for Pa_{O_2} was less when the response was depressed by isoprenaline and the high dose of dopamine than during the other hypoxic periods.

One of the problems inherent in this type of animal model is that the magnitude of the response varies widely between animals and usually increases with time. The increase with time was observed in a number of our earlier studies (Sykes, Hurtig et al., 1977b) and was thought to result from the administration of drugs, for there had been no increase in the response in four dogs which has been subjected to unilateral hypoxia every 30 min for 2 h without the administration of drugs. However, an increase in the response with time was observed later in five other dogs studied over a period of 4 h, whilst Unger and colleagues (1977) have now confirmed that the response increases with time in the absence of drug administration. On account of this poor initial response and the relatively short half-life of the drugs we decided to adopt a programme in which the smallest dose of dopamine was always given first. Unfortunately, the failure to randomize the sequence of the administration of the drugs created further problems because the control values for cardiac output after the smaller dose of dopamine were significantly less than during the initial control period. The reduction in cardiac output after dopamine has been observed in other experiments in which the animals were not submitted to hypoxia and is associated with changes in glucose and fat metabolism (G. M. Hall, personal communication). Also, it has been seen frequently in the clinical situation when the rate of infusion of the drug is reduced suddenly.

Although the significance of the results with the low dose of dopamine is open to question, there was a marked depression of the hypoxic response during the administration of the high dose of dopamine and during the administration of isoprenaline. The latter observation confirms previous studies which showed that isoprenaline 0.1 μg kg^{-1} min^{-1} depressed the response in dogs (Hill and colleagues, personal communication).

A decrease in hypoxic vasoconstriction may result from altered transpulmonary or vascular pressures, changes in blood flow, changes in vasomotor tone or from a direct action of the drug on the hypoxic vasoconstrictor mechanism. Although there were significant increases in the airway pressure on the left side during unilateral hypoxia the magnitude of the changes was small and certainly not great enough to modify the magnitude of the response. Cardiac output was increased significantly by both isoprenaline and the high dose of dopamine, but although there were significant increases in mean pulmonary artery pressure with both drugs the magnitude of the changes was small. Changes in left atrial pressure were minimal also. Benumof and Wahrenbrock (1975) have shown that increases in lung vascular pressures can depress the magnitude of the hypoxic reponse but they observed a decrease in the response only when the changes in pressures were much greater than those recorded in this study.

Furthermore, mean pulmonary artery and pulmonary wedge pressures during C_4 were similar to those during the infusions of the drugs and large diversions of flow were recorded at this time. Therefore, it seems unlikely that the response could have been depressed by the haemodynamic changes accompanying the administration of the drugs.

Changes in vasomotor tone during the infusions of the drugs could have modified the responses to hypoxia by altering the Laplace relationship so it is necessary to consider the effects of the drugs on pulmonary vascular resistance. Unfortunately, the changes in cardiac output in the present experiments render the interpretation of the measurements of pulmonary vascular resistance difficult. It is well known that measured pulmonary vascular resistance decreases with increasing blood flow and with increasing vascular pressures because of recruitment and passive distension of the pulmonary vascular bed (Rudolph and Auld, 1960). Evidence from lung perfusion experiments in which these variables can be controlled is open to suspicion because the initial vascular tone appears to differ widely between individuals. As a result, drugs which have both dilator and constrictor actions on the vascular bed may appear to be predominantly dilator in some individuals and constrictor in others. Nevertheless, it is generally agreed that isoprenaline is a powerful vasodilator in the dog (Aviado and Schmidt, 1957) whilst dopamine is a vasoconstrictor (Waaler, 1961; Mentzer, Alegre and Nolan, 1976). Since the hypoxic vasoconstrictor response was depressed by both drugs it seems unlikely that the effect could have been a result of changes in vasomotor tone. Furthermore, vasomotor changes induced by the drugs would have affected each lung equally and so should not have affected the distribution of flow. Therefore it seems reasonable to conclude that the drugs had a specific effect on the pulmonary vasoconstrictor mechanism. Since the mechanisms underlying this response are still unknown (Hales, Rouse and Kazemi, 1977) there is little to be gained from a consideration of how the drugs may diminish the response.

The redistribution of blood flow in response to unilateral hypoxia was accompanied by a decrease in end-tidal carbon dioxide on the hypoxic side and an increase on the oxygenated side, but the magnitude of these changes was reduced when the redistribution of flow was reduced during the administration of the drug. These measurements confirm the radioisotope measurements. They may also explain the increase in peak and end-inspiratory airway pressures on the left side during unilateral hypoxia, for Patterson (1972) has demonstrated that a reduction in end-tidal carbon dioxide causes an increase in airway resistance in dogs. It is unlikely that the variations in end-tidal $P\text{CO}_2$ had a significant effect on the magnitude of the response (Malik and Kidd, 1973). Therefore the changes in carbon dioxide would have tended to oppose the observed changes in blood flow.

The observed differences in arterial $P\text{O}_2$ during unilateral hypoxia correlate also with the changes in blood flow and indicate how arterial $P\text{O}_2$ may be reduced in the clinical situation. Ideally, the experimental model should have enabled us to examine the blood flow through an atelectatic zone of lung. However, there are technical difficulties in the use of electromagnetic flow probes in such situations and we chose to use a method of measuring regional pulmonary blood flow which did not involve thoracotomy or any mechanical interference with the pulmonary circulation. Since this method depended on the elimination of xenon-133 from the alveoli the response had to be induced by decreasing the inspired oxygen concentration. In previous experiments we have used ventilation with nitrogen 100% as the hypoxic stimulus. This gas provides a more powerful stimulus than oxygen 7% but decreases end-pulmonary capillary $P\text{O}_2$ below that of mixed venous. Since the extraction of oxygen from the mixed venous blood during nitrogen inhalation depends on the ventilation/perfusion ratio, the end-pulmonary capillary $P\text{O}_2$ in the hypoxic lung is lower when blood flow is maximally diverted and blood flow through the hypoxic lung is decreased. Thus, Pa_{O_2} values during unilateral hypoxia with nitrogen underestimate the magnitude of the redistribution of blood flow.

We chose, therefore, to use a hypoxic mixture which had been shown in previous experiments to produce an end-capillary $P\text{O}_2$ close to the normal mixed venous value. With this mixture the decrease in arterial $P\text{O}_2$ when the response is completely abolished is similar to that which might occur in the clinical situation when the right-to-left shunt flow through an atelectatic lung is approximately equivalent to 45% of the cardiac output.

Although the present experiments suggest that both dopamine and isoprenaline may cause arterial hypoxaemia by depressing the hypoxic vasoconstrictor response, this mechanism can only be of importance when there are significant areas of regional underventilation. Hypoxaemia has been noted to occur in dogs with normal lungs when isoprenaline has been infused (Finlay, Wightman and Sykes, 1970; Loh, Seed and Sykes, 1971), but not when dopamine has been given (Scott, Chakrabarti and Hall, in preparation). Therefore, other mechanisms causing hypoxaemia must be considered. There are two main possibilities.

In the first place the increase in cardiac output in the presence of a fixed ventilation might alter the overall ventilation/perfusion ratio and so cause a decreased arterial Po_2. This mechanism was observed during isoprenaline infusion (Finlay, Wightman and Sykes, 1970) but it was found in these studies that, when Pco_2 was kept at control values during the infusion of the drug by increasing either tidal volume or frequency, there was still an increase in total venous mixture (breathing air) and an increase in shunt (breathing oxygen 100%) as the dosage of isoprenaline was increased. This suggested that the isoprenaline must have opened previously closed right-to-left shunt pathways. Since a direct relationship between shunt and cardiac output has been observed when output was changed by both haemorrhage and transfusion and by a wide variety of drugs (Yamamura et al., 1969; Sykes et al., 1970; Watanabe et al., 1970) it seems likely that the changes are mainly a result of altered haemodynamics or of changes in mixed venous Po_2 and not of specific actions of the drugs on the shunt pathways (Smith, Cheney and Winter, 1974).

It is concluded that there are a number of possible mechanisms which may account for the reduction in arterial Po_2 noted during the administration of isoprenaline and dopamine. In most patients arterial hypoxaemia can be avoided by increasing the inspired Po_2 and by increasing ventilation to match the increased carbon dioxide production. However, in patients with severe lung disease these drugs may produce dangerous arterial Po_2 values. The present experiments suggest that, for a given increase in inotropic activity, the two drugs produce a similar amount of depression of the hypoxic vasoconstrictor mechanism. However, the choice of an inotropic drug must be based on a consideration of many other factors and must finally be decided by studies on patients.

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DEPRESSION DE LA VASOCONSTRICTION PULMONAIRE HYPOXIQUE CHEZ LE CHIEN PROVOQUEE PAR LA DOPAMINE ET L'ISOPRENALINE

RESUME

Les effets de la dopamine et de l'isoprénaline sur la réaction vasoconstrictrice pulmonaire à l'hypoxie alvéolaire ont été évalués en mesurant la redistribution du débit sanguin entre les poumons par suite de la réaction à l'hypoxie unilatérale. Les doses de dopamine: 25 $\mu g\ kg^{-1}\ min^{-1}$ et d'isoprénaline: 0,25 $\mu g\ kg^{-1}\ min^{-1}$ (qui produisent des augmentations équivalentes de la force contractile du coeur des chiens) ont produit un degré similaire de dépression de la réaction vasoconstrictrice hypoxique, alors que des doses de dopamine de 2,5 $\mu g\ kg^{-1}\ min^{-1}$ n'ont eu que peu d'effet sur la réaction. Pendant l'hypoxie unilatérale, la Pa_{CO_2} a eu une réaction inverse au débit sanguin par l'intermédiaire du poumon hypoxique.

SCHWÄCHUNG DER LUNGENGEFÄSS-VERENGUNG BEI MANGELHAFTER OXIDATION IM HUND DURCH DOPAMIN UND ISOPRENALIN

ZUSAMMENFASSUNG

Der durch Dopamin und Isoprenalin auf die Reaktion des Lungengefässkonstriktors auf alveolären Oxidationsmangel ausgeübte Einfluss wurde durch Messen der Wiederverteilung des Blutflusses zwischen den Lungenflügeln als Reaktion auf einseitige Hypoxie abgeschätzt. Dosierungen von 25 $\mu g\ kg^{-1}\ min^{-1}$ Dopamin und 0,25 $\mu g\ kg^{-1}\ min^{-1}$ Isoprenalin (die die gleichen Zuwachsraten in der Herzkontrakturkraft in Hunden hervorriefen) erzielten eine ähnliche Herabsetzung in der Vasokonstriktorreaktion bei Oxidationsmangel, 2,5 $\mu g\ kg^{-1}\ min^{-1}$ Dopamin jedoch hatten nur geringen Einfluss auf die Reaktion. Wahrend einseitiger Hypoxie standen die arteriellen Lungensauerstoffwerte im umgekehrten Verhältnis zum Blutfluss durch den unter Oxidationsmangel stehenden Lungenflugel.

DEPRESION DE LA VASCONSTRICCION PULMONAR HIPOXICA EN EL PERRO MEDIANTE DOPAMINA E ISOPRENALINA

SUMARIO

Se evaluaron los efectos ejercidos por dopamina e isoprenalina sobre la respuesta vasconstrictora pulmonar a la hipoxia alveolar, midiendo la redistribución de la circulación sanguínea entre los pulmones, producida como respuesta a la hipoxia unilateral. Las dosis de nivel 25 $\mu g\ kg^{-1}\ min^{-1}$ de dopamina y 0,25 $\mu g\ kg^{-1}\ min^{-1}$ de isoprenalina (que produjeron incrementos iguales en la fuerza contráctil del corazón en perros) produjeron un grado semejante de depresión de la respuesta vasconstrictora hipóxica, mientras que 2,5 $\mu g\ kg^{-1}\ min^{-1}$ de dopamina ejerció poco efecto sobre la respuesta. Durante la hipoxia unilateral, el Pa_{O_2} se relacionó inversamente con la circulación de la sangre a través del pulmón hipóxico.

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COMPARISON OF FLUNITRAZEPAM AND DIAZEPAM FOR ORAL PREMEDICATION IN OLDER CHILDREN

F. J. RICHARDSON AND M. L.-M. MANFORD

SUMMARY

A double-blind trial was conducted of two benzodiazepines, flunitrazepam and diazepam, given orally to 142 children (30 kg in weight or heavier) undergoing routine surgery. Flunitrazepam was associated with greater sedation before operation and less vomiting after operation than diazepam. Flunitrazepam caused a greater frequency of amnesia for the periods of induction and immediately after operation. Plasma concentrations were measured in 65 children and were found to be significantly greater in those children having amnesia for the induction period in both flunitrazepam and diazepam groups. In the diazepam group, plasma concentrations were significantly smaller in those who vomited than in those who did not vomit.

Children are premedicated frequently with a combination of an opiate and an anticholinergic agent parenterally. This is unpopular with the children and unneccessary unless pain relief is required or unless premedication by the oral route is contraindicated. Dundee, Loan and Morrison (1970) demonstrated that the more commonly used opiates were far from satisfactory and they suggested that diazepam might be superior for premedication under appropriate conditions. Steen and Hahl (1969) had found diazepam to be almost ideal for pre-anaesthetic medication, and Haq and Dundee (1968) reported that diazepam was as effective as trimeprazine in children.

Flunitrazepam (Ro. 05–4200) is a newer member of the benzodiazepine group of drugs and is thought to have superior tranquillizing and amnesic qualities. When used as an i.v. induction agent the equivalent doses of flunitrazepam to diazepam were considered to be 10 : 1 (Vega, 1971; Stovner, Endresen and Osterud, 1973; Pearce, 1974; Dundee et al., 1976) and, as a direct comparison of the oral doses of flunitrazepam and diazepam could not be found, the same ratio was used in this trial. The present study was undertaken to compare the two drugs as premedicants.

Previous studies with diazepam have shown little correlation between blood concentrations and clinical effect (Haffner et al., 1973; Ghoneim, Mewaldt and Ambre, 1975) and we studied this aspect again.

METHODS

One hundred and forty-two children (weighing 30 kg or greater) undergoing various types of general surgery were included in a trial at Queen Mary's Hospital for Children, Carshalton. Emergency cases and patients considered unsuitable for oral premedication, such as severely mentally retarded children, were excluded. The children were allocated to three weight groups: 31–40 kg, 41–50 kg, 51 kg and more; these groups received flunitrazepam or diazepam randomly in doses of 1, 1.5, 2 mg of flunitrazepam respectively or 10, 15, 20 mg of diazepam. The drugs were supplied as identical tablets in envelopes marked only with the weight group and numbered from random tables according to the order in which they were to be used for each weight group. Neither the medical nor the nursing staff knew which drug any child received.

The oral premedication was given approximately 90 min before operation. Atropine was not given. The effectiveness of the premedication was based on Doughty's method (Doughty, 1959, 1962). On arrival in the anaesthetic room, the child's mental state was assessed by one of us as "satisfactory" if the patient was asleep, drowsy or alert and calm, and as "unsatisfactory" if apprehensive, tearful or uncooperative. The reaction to induction of anaesthesia, with i.v. thiopentone or by inhalation, usually with halothane in a mixture of nitrous oxide in oxygen, was assessed as "satisfactory" if the child made no

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response, winced briefly, withdrew his hand but remained co-operative, or only turned his face away from the mask. Conditions were "unsatisfactory" if the child became obviously upset, cried or became unco-operative. The presence of excessive secretions in the mouth was noted at the time of induction. Initially atropine was given i.v. at induction to children undergoing otolaryngological surgery or other procedures requiring tracheal intubation. However, as the trial progressed this was not considered necessary and subsequently it was given only if a child required pharyngeal suction because of excess secretions. Anaesthesia was maintained usually with halothane in nitrous oxide in oxygen, although occasionally diethyl ether or trichloroethylene was used. After operation the children were returned to the recovery ward where the recovery time (able to give his or her name), and the occurrence of vomiting, pallor or other untoward events was noted by the same team of nursing staff. The following day one of the authors assessed amnesia and noted any comments by the child.

Venous blood was sampled from 65 of the children after anaesthesia had been induced and plasma drug concentrations were determined by electron-capture gas–liquid chromatography. For flunitrazepam the method of de Silva and Bekersky (1974) was used with small modifications. The borate buffer was replaced by 20% ammonium chloride pH 9.2 buffer, tolune was used in place of benzene in the extracting solvent and methylclonazepam was used as the internal standard. Diazepam was assayed by the method of Zingales (1973) with the addition of prazepam as internal standard.

The results were analysed statistically using two-sided tests at the 5% level of significance (the χ^2 test where numbers were large enough and Fisher's exact probability test otherwise for the clinical results in tables I and II, and Student's t test for the drug concentration data in table III).

RESULTS

Of the 142 children in the trial, 70 received diazepam and 72 flunitrazepam (of whom one had a change of plaster without anaesthesia). The numbers of children judged to have unsatisfactory premedication by a variety of criteria are shown in table I.

Mental state

In each group there was a greater number of children in whom the mental state was unsatisfactory after diazepam than after flunitrazepam. The difference was only statistically significant when the three groups were combined ($P < 0.05$). This combination was justified as the numbers of children in the two drug groups could be matched within each weight group and the "unsatisfacory" proportion was similar in the three groups. Overall, in the flunitrazepam group 99% were considered to be in a satisfactory mental state before operation, compared with 89% in the diazepam groups.

Response to induction of anaesthesia

There was no significant difference between the two drug groups, 99% of the flunitrazepam group

TABLE I. *Children showing undesirable effects (U), and total numbers for whom information was available.* (** $P < 0.05$)

	Mental state before op.		Reaction to induction		Salivation		Vomiting		Pallor	
Weight	U	Total	U	Total	U	Total	U	Total	U	Total
30–40 kg										
Flunitrazepam	1	33	1	32	8	32	10	32	3	32
Diazepam	4	32	2	32	9	32	10	32	0	32
41–50 kg										
Flunitrazepam	0	26	0	26	5	26	6	26	2	26
Diazepam	3	25	3	25	11	25	12	25	1	25
> 50 kg										
Flunitrazepam	0	13	0	13	4	13	0	13	0	13
Diazepam	1	13	0	13	6	13	5	13**	0	13
Total										
Flunitrazepam	1	72	1	71	17	71	16	71	5	71
Diazepam	8	70**	5	70	26	70	27	70	1	70

and 93% of the diazepam group having a satisfactory response.

Salivation

This was assessed at induction as excessive and unsatisfactory if the pharynx was more than moist. Similar numbers of children in both groups received atropine. There was no significant influence associated with flunitrazepam as compared with diazepam, although each group contained more "unsatisfactory" results after diazepam. Seventy-six per cent of children in the flunitrazepam group and 63% in the diazepam group were classified as satisfactory.

Vomiting

A total of 49 children vomited. Two of these vomited only briefly immediately after the tracheal tube was removed and they were considered to have done so as a result of "gagging" on the tube; four vomited in the late evening (more than 4 h after operation) and this was attributed to analgesics administered after operation. Thus 43 children suffered vomiting which was regarded as being associated with anaesthetic drugs. Cyclopropane was used for induction in eight patients, vomiting occurring afterwards in one of these. Trichloroethylene was used during maintenance of anaesthesia in seven patients, only one of whom vomited subsequently. Of eight children in whom ether in nitrous oxide in oxygen maintenance was used, five vomited, and four of these were undergoing adenotonsillectomy.

The difference in the frequency of vomiting in the two drug groups was statistically significant at the 5% level in children weighing more than 50 kg.

Overall vomiting occurred in 23% of the flunitrazepam group and 39% of the diazepam group. After exclusion of those undergoing adenotonsillectomy the respective proportions were 18% and 35% (10 children of 55 in the flunitrazepam group and 18 of 52 in the diazepam group).

Pallor

This was noted in the recovery period in six children, five of whom had received flunitrazepam (7%).

Amnesia (table II)

Not all the children were available for interview on the day following operation.

Children were described as having amnesia for the induction of anaesthesia if they had no recall of the trolley ride to the anaesthetic room, of conversation before induction and of the type of induction. Amnesia for the period immediately after operation was noted if the child could not remember waking in the recovery ward, vomiting or the time of wakening. Several children were recorded as being alert for a period about which they could remember nothing.

TABLE II. *Numbers of children having amnesia for the periods of induction and immediately after operation and total for whom information was available*

Weight	Induction		After operation	
	Amnesia	Total	Amnesia	Total
30–40 kg				
Flunitrazepam	16	27	17	22
Diazepam	6	22	9	20
Difference between drugs	$P < 0.05$		$P < 0.05$	
41–50 kg				
Flunitrazepam	20	22	13	16
Diazepam	9	19	8	16
Difference between drugs	$P < 0.01$		n.s.	
>50 kg				
Flunitrazepam	10	13	8	9
Diazepam	4	8	4	7
Difference between drugs	n.s.		n.s.	
Total				
Flunitrazepam	46	62	38	47
Diazepam	19	49	21	43
Difference between drugs	$P < 0.001$		$P < 0.01$	

A greater proportion of children receiving flunitrazepam had amnesia for induction ($P < 0.001$) and the period after operation ($P < 0.01$) (for induction after flunitrazepam 74%, diazepam 39%, for postoperative events 81% and 49% respectively).

Other effects

Restlessness was noted by the recovery ward staff in 28 children; 13 had received flunitrazepam and 15 diazepam. This was often relieved within a short time of giving an analgesic, but data are incomplete. No nystagmus, double-vision or ataxia was noted, nor any other untoward effects which might have resulted from the premedication.

Drug concentrations in plasma (table III)

The time interval between ingestion of the tablets and taking the blood sample varied (50–170 min in the flunitrazepam group and 75–175 min in the diazepam group). No allowance for the variable sampling time was made in the statistical analysis.

TABLE III. *Plasma concentration of flunitrazepam and diazepam in relation to amnesia and vomiting*

	Flunitrazepam						Diazepam					
	Plasma concn. (ng ml^{-1})			Time from ingestion to sampling (min)			Plasma concn. (ng ml^{-1})			Time from ingestion to sampling (min)		
	n	Mean	SD	Mean	SD	Range	*n*	Mean	SD	Mean	SD	Range
Totals for all children sampled	34	9.4	3.1	117.8	28.3	50–170	31	176.4	76.8	120.2	21.4	75–175
No amnesia for induction	11	7.4	2.6	112.3	35.3		18	148.3	54.5	127.5	29.1	
Amnesia for induction	20	10.2	3.2	123.5	25.0		6	240.5	103.2	115.0	11.8	
Difference	$0.01 < P < 0.025$						$P < 0.01$					
No amnesia for post-op. period	3	7.8	1.4	106.7	17.6		12	180.8	87.2	120.4	24.1	
Amnesia for post-op. period	19	9.6	2.3	122.4	32.6		9	162.6	78.0	131.7	30.6	
Difference	$P > 0.10$						$P > 0.10$					
Not vomiting	27	9.9	3.3	116.7	30.3		21	197.6	83.5	116.0	24.2	
Vomiting	6	7.4	1.1	115.8	11.6		10	132.0	30.8	129.0	27.8	
Difference	$P > 0.05$						$0.01 < P < 0.025$					

Plasma concentrations of both flunitrazepam and diazepam were significantly greater in those children who had amnesia for the induction period compared with those who had no amnesia. There was no relationship between amnesia for the period after operation and the plasma concentration.

The children in the diazepam group who vomited after operation had significantly smaller plasma concentrations than those who did not vomit. Those vomiting in the flunitrazepam group also had smaller plasma concentrations but the difference was not statistically significant.

There was no correlation between drug concentrations and the other clinical criteria assessed, nor was there any significant relationship between drug concentrations and the use of atropine or different anaesthetic techniques.

DISCUSSION

The sedative and anxiolytic effects of the benzodiazepines (Dundee and Haslett, 1970) are very useful especially when analgesia before operation is not required, as is the case with most routine surgery.

The oral route of drug administration is much more acceptable to children and to their nurses. For heavier children large volumes of syrups and suspensions are required and these preparations are frequently bitter and often rejected. For these reasons we used tablets and few children refused their premedication in this form; only one had to be excluded from the trial because of vomiting before anaesthesia.

Our results show that both flunitrazepam and diazepam give satisfactory sedation before operation and response to induction, flunitrazepam producing slightly better conditions than diazepam.

The amount of salivation after premedication with diazepam has often been reported as greater than after other drugs (Haq and Dundee, 1968; Boyd and Manford, 1973). In this trial salivation was considered unsatisfactory in 37% after diazepam and in 24% after flunitrazepam. Only 40% of the children received atropine i.v. at or after induction of anaesthesia. There were, however, no serious sequelae in the 60% who did not. Atropine may delay gastric emptying and the absorption of oral drugs (Gamble, 1975) and perhaps reduce the muscle tone of the lower oesophageal sphincter (Brock-Utne et al., 1976).

There are many reports of the amnesic properties of the benzodiazepines, particularly following i.v. administration (Stovner and Endresen, 1966; Heisterkamp and Cohen, 1975; George and Dundee, 1977). Lorazepam has been reported to produce amnesia following oral administration when diazepam in the doses of 10–20 mg did not (Harry and Richards, 1971; Wilson and Ellis, 1973). We found a high frequency of amnesia for the induction period with both oral flunitrazepam and diazepam (74 and 39% respectively) and also for the period after operation

(81 and 49% respectively). This high frequency may reflect the doses used; indeed the mean plasma drug concentrations were significantly greater in those with amnesia for the preoperative–induction period than in those with no impairment of recall. The overall mean plasma concentration of 176.4 ng ml^{-1} (SD 76.8) for diazepam was similar to that found in previous studies of adults (Gamble, Dundee and Assaf, 1975; Nair et al., 1976). Our mean concentration was relatively small despite much greater doses (mean 0.3 kg^{-1} body weight for those who had blood samples taken) and this is probably a reflection of the longer time between ingestion and blood sampling (mean 120.2 min, SD 21.4). In both the reports cited the peak plasma concentrations occurred at 60 min. Even so, our group with amnesia had a greater mean plasma concentration than the patients reported in earlier studies. Thus, higher oral dosage may be indicated if it is regarded as desirable to have amnesia for the period of induction.

In most of the earlier studies in which no significant amnesia was found with diazepam and in which no plasma concentrations had been measured, atropine had been used in the premedication. I.v. or i.m. atropine has been found to result in smaller plasma concentrations of diazepam after oral administration of the drug (Gamble et al., 1976).

We found no significant difference between plasma concentrations of both drugs in children who did or did not experience amnesia for the period immediately after operation. The part played by drug metabolites is unknown as only plasma concentrations of flunitrazepam and diazepam themselves were measured. Two of the metabolites of diazepam, N-desmethyldiazepam and oxazepam, are known to have psychopharmacological activity. The effects of metabolites of diazepam and flunitrazepam may be part of the explanation for the lack of correlation between the drug concentrations measured and the high frequency of amnesia after operation. Against this is the slow rate of metabolism of diazepam (half-life 20–40 h), although Baird and Hailey (1973) reported small amounts of N-desmethyldiazepam in blood 60–90 min after i.m. diazepam. Garattini and others (1973) advanced other explanations for the lack of correlation of plasma concentrations of benzodiazepines and their clinical effects, including the inconstancy of the relationship between blood and brain concentrations, the variable distribution of benzodiazepines in different areas of the brain and differing pharmacological effects of different blood or brain concentrations.

Amnesia for possibly unpleasant events before and after anaesthesia and surgery can be of great value, especially in highly impressionable children. In this context the benzodiazepines have a great advantage over many other premedicant drugs. However, prolonged amnesia after operation (several of our patients could remember nothing for several hours after surgery) is undesirable for outpatients, and may be indicative of depression of other "central" functions. We saw no clinical signs of the latter. Indeed, the children in the trial seemed to be alert very quickly after operation, including those who were later found to be amnesic for that time.

Those vomiting after operation and who had received diazepam had significantly smaller plasma concentrations. One may speculate that those not vomiting were protected by a specific anti-emetic effect of the greater plasma concentration of diazepam or that there was less likelihood of vomiting from anxiety.

Korttila and Linnoila (1975) showed that diazepam was "most harmful to co-ordination" for several hours after i.v. injection, and inco-ordination or ataxia has been reported also after lorazepam (Dodson et al., 1976). We found no nystagmus or evidence of double vision or inco-ordination after operation, but our patients were kept in bed and no specific tests of co-ordination were used. Three of our patients said they felt dizzy.

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COMPARAISON DU FLUNITRAZEPAM ET DU DIAZEPAM COMME PREMEDICATIONS ORALES CHEZ LES GRANDS ENFANTS

RESUME

On a procédé à une étude à double inconnue sur deux benzodiazépines: le flunitrazépam et le diazépam, administrés oralement à 142 enfants (pesant 30 kg et plus), devant subir une intervention chirurgicale ordinaire. Le flunitrazépam a été associé à une plus forte sédation avant l'opération et à moins de vomissements aprés l'opération que le diazépam. Le flunitrazépam a causé une plus grande fréquence d'amnésie pendant la période d'induction et immédiatement après l'opération. Les concentrations dans le plasma ont été mesurées sur 65 enfants et on a trouvé qu'elles étaient beaucoup plus fortes chez les enfants ayant eu une amnésie pendant la période d'induction et ce aussi bien pour le groupe flunitrazépam que pour le groupe diazépam. Dans le groupe diazépam, les concentrations dans le plasma ont été beaucoup moins importantes chez ceux qui ont vomi que chez ceux qui n'ont pas eu de vomissements.

VERGLEICH VON FLUNITRAZEPAM UND DIAZEPAM FÜR MÜNDLICHE VORBEHANDLUNG BEI ÄLTEREN KINDERN

ZUSAMMENFASSUNG

Mit zwei Benzodiazepinen, Flunitrazepam und Diazepam, die 142, sich routinemässiger Chirurgie unterziehenden Kindern (30 kg schwer oder schwerer) mündlich eingegeben wurden, wurde ein Doppelblindversuch durchgeführt. Flunitrazepam war präoperativ mit grösserer Beruhigung und postoperativ mit geringerem Erbrechen verbunden als Diazepam. Flunitrazepam verursachte eine grössere Amnesiehäufigkeit fur die Induktionszeiten und unmittelbar nach der Operation. Plasmakonzentrationen wurden in 65 Kindern gemessen und lagen bedeutend höher in den für die Induktionszeit an Amnesie leidenden Kindern, sowohl in der Flunitrazepam- als auch in der Diazepamgruppe. In der Diazepamgruppe waren die Plasmakonzentrationen bedeutend niedriger in denen, die sich erbrachen als in denen, die sich nicht erbrachen.

COMPARACION ENTRE FLUNITRAZEPAM Y DIAZEPAM PARA PREMEDICACION ORAL EN NINOS MAYORES

SUMARIO

Se condujo una prueba de doble anonimato con dos benzodiazepinas, flunitrazepam y diazepam, administrados oralmente a 142 niños (de 30 kg de peso o más), sometidos a cirugía de rutina. El flunitrazepam fue asociado con una mayor sedación anterior a la operación y menos vómitos después de la operación, que con el diazepam. El flunitrazepam provocó una mayor frecuencia de amnesia para los períodos de inducción e inmediatamente después de la operación. Se midieron las concentraciones en la plasma de 65 niños, descubriéndose que eran significativamente superiores en aquellos niños que sufrieron amnesia durante período de inducción, tanto en el grupo de diazepam como en el de flunitrazepam. En el grupo de diazepam, las concentraciones de plasma fueron significativamente inferiores entre aquellos que vomitaron que entre aquellos que no vomitaron.

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COMPARISON OF I.M. PETHIDINE, DIAZEPAM AND FLUNITRAZEPAM AS PREMEDICANTS IN CHILDREN UNDERGOING OTOLARYNGOLOGICAL SURGERY

L. Lindgren, L. Saarnivaara and J.-J. Himberg

SUMMARY

Pethidine 1 mg kg^{-1}, diazepam 0.25 mg kg^{-1} and flunitrazepam 0.02 mg kg^{-1} i.m. were compared as premedicants in a double-blind study in 145 children undergoing otolaryngological surgery. Both flunitrazepam and pethidine had an anxiolytic effect in the children of less than 5 yr whereas diazepam had little effect. All of the drugs were anxiolytic in the children aged 5 yr and older. Sleep following thiopentone was restless more often in the younger than in the older children. Cardiovascular responses to thiopentone and to tracheal intubation were most obvious following benzodiazepines in children of less than 5 yr. After anaesthesia 20–33% of the older children could not recall pictures shown to them before anaesthesia. Forty-five (± SD 13) min after injection, the concentration of diazepam in serum was similar in both age groups; after 90 min it decreased in the younger and increased in the older children. All concentrations of flunitrazepam were significantly greater in the older compared with the younger children.

Premedication is specially important in children, in whom separation from parents and fear of medical procedures may cause apprehension of a degree which can cause psychiatric disturbances after operation (Eckenhoff, 1953). Children undergoing adenotonsillectomy may have suffered several episodes of illness, rendering them fearful and irritated.

Haq and Dundee (1968) have shown that preoperative apprehension in children, with crying and tachycardia, increases bleeding during adenotonsillectomy. They found oral diazepam and trimeprazine to be equally satisfactory as premedicants. In our practice we have used i.m. pethidine or, occasionally, diazepam. These drugs usually seem to be satisfactory for older children, but not for younger children.

The present study was designed to compare i.m. pethidine, diazepam or flunitrazepam as premedicants in children undergoing otolaryngological surgery, mostly adenotonsillectomy. Flunitrazepam was included because of its sedative and amnesic properties (Dundee, George et al., 1976; Korttila et al., 1978).

PATIENTS AND METHODS

Patients and assessment of premedication

One hundred and forty-five unselected children aged 0–15 yr were premedicated with pethidine (Petidin, Star, Tampere) 1 mg kg^{-1} or diazepam (Diapam, Orion, Helsinki) 0.25 mg kg^{-1} or flunitrazepam (Rohypnol, Roche, Basel) 0.02 mg kg^{-1} all in combination with atropine (Atropin, Orion, Helsinki) 0.02 mg kg^{-1} injected into the gluteal muscle 45 (± 13 SD) min before the start of anaesthesia. The children were allocated at random to one of the three premedicant groups.

TABLE I. *Anxiolysis score immediately before the start of anaesthesia. Total scores: 0–1 = poor, 2–3 = fair, 4–5 = good, 6–7 = excellent*

	Score
Behaviour of child	
Crying or struggling	0
Calm	1
Sedated	2
Drowsy	3
Sleeping but arousable	4
Reaction to venepuncture	
Crying or struggling	0
Wincing or vocalizing	1
Moving the hand	2
None	3

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After the child's arrival in the operating room his behaviour was assessed and scored by one of the authors (L. L.) who anaesthetized all the children without knowing the premedicant. The scoring of the effects of premedication (table I) was a modification of the method of Barker and Nisbet (1973). Relief of anxiety was *poor* if the score was 0–1, *fair* 2–3, *good* 4–5 and *excellent* 6–7. After studying about 10 children a significant difference was apparent between the children older and younger than 5 yr and we separated and compared these two age groups.

Table II shows time between the i.m. injection of the premedicant and scoring of anxiety, and the sampling of blood for measurement of drug concentrations.

TABLE II. *Time interval between the i.m. injection of the premedicants and scoring of their anxiolytic effects, and the assessment of their concentration in serum (mean interval* = 45 (±13) *min)*

Treatment group	Interval (min ± SD)
Children less than 5 yr	
Pethidine	47.4 ± 11.8
Diazepam	42.9 ± 11.5
Flunitrazepam	45.2 ± 12.5
Children older than 5 yr	
Pethidine	41.3 ± 13.2
Diazepam	45.2 ± 13.6
Flunitrazepam	48.4 ± 13.4

Assessment of amnesia

Two pictures were shown before the start of anaesthesia. Children less than 10 yr were shown and asked to identify pictures of a flower and a house and those more than 10 yr saw pictures of a shoe and a car. At 2 and 24 h after operation they were asked to recall the pictures.

Anaesthesia

Anaesthesia was induced with thiopentone 5 mg kg^{-1} given over 45 s. Except for children undergoing tympanotomy, the trachea was intubated following suxamethonium 1.5 mg kg^{-1}. The intensity of muscle fasciculations was noted. Anaesthesia was maintained with halothane (commencing with 2% and reducing gradually thereafter in 70% nitrous oxide in oxygen. A Rees system was used for children weighing less than 25 kg and a circle system with carbon dioxide absorption for those more than 25 kg. Ventilation was assisted or controlled. The arterial systolic pressure was measured indirectly and the heart rate was counted using a praecordial stethoscope before and after injection of thiopentone, 30 s after intubation and every 5 min during the operation. Side-effects were noted.

Assessment of drug concentrations in serum

Venous blood was sampled 45 ± 13 and 90 min after the injection of diazepam and flunitrazepam. The first sample was drawn from the needle inserted for the induction injection before the start of anaesthesia and the second sample from the same needle in the recovery room. Sera were stored at −22 °C until analysed for diazepam content by the method of de Silva and others (1976) and for flunitrazepam by the method of de Silva and Bekersky (1974). In both methods a Hewlett-Packard model 5830A gas chromatograph with electron capture detector and 7671A automatic sampler was used. A 1.2-m glass column with an internal diameter of 4 mm was packed with 3% OV 225 on 80/100-mesh chromosorb W AW DMCS. The carrier gas was 90% argon in methane filtered through a molecular sieve and at a rate of 50 ml min^{-1}. Operating temperatures were: injector 270 °C, column 245 °C for diazepam and 250 °C for flunitrazepam, detector 325 °C. Under these conditions the retention times were 1.2 min for medazepam, 3.2 min for diazepam, 6.5 min for flunitrazepam and 11.5 min for n-desmethylflunitrazepam. The sensitivity limit was 5 ng ml^{-1} for diazepam and 1 ng ml^{-1} for flunitrazepam when a 1-ml sample of serum was used.

Student's *t* test was used for parametric data and the Mann–Whitney test for non-parametric data.

RESULTS

Table III shows that with regard to sex, physical condition, age, weight and blood concentration of haemoglobin the groups less than and more than 5 yr were comparable.

Figure 1 shows that both flunitrazepam and pethidine had an anxiolytic effect in the children less than 5 yr whereas the effect of diazepam was poor in this age group. Flunitrazepam differed significantly from diazepam. All premedicants produced a good anxiolytic effect in the children older than 5 yr. The anxiolytic effect of each drug was significantly better in the children 5 yr and more than in those less than that age.

Table IV shows that in all premedicant groups sleep following thiopentone was more often restless (child crying or moving) in the younger (25–55%)

TABLE III. *Characteristics of premedicant groups. Mean value ± SD. Number of children in parentheses*

Premedicant group	Male/Female	Physical condition good/moderate	Mean age (yr)	Weight (kg)	Haemoglobin concn (g litre^{-1})
Less than 5 yr					
Pethidine (17)	11/6	14/3	3.5 ± 1.1	15.7 ± 4.1	126.4 ± 10.6
Diazepam (20)	13/7	20/0	3.6 ± 1.1	14.0 ± 3.3	124.0 ± 8.4
Flunitrazepam (20)	12/8	16/4	3.6 ± 1.2	12.7 ± 2.7	126.5 ± 8.1
5 yr and more					
Pethidine (32)	17/15	26/6	8.4 ± 2.7	28.0 ± 9.7	133.4 ± 5.9
Diazepam (26)	13/13	22/4	8.6 ± 2.9	29.6 ± 9.4	132.7 ± 7.9
Flunitrazepam (30)	20/10	27/3	8.2 ± 2.4	25.9 ± 7.6	130.6 ± 7.7

TABLE IV. *Frequency (%) of induction characteristics using different premedicants. Number of children in parentheses. Premedicant groups different from children less than 5 yr: † $P < 0.02$; †† $P < 0.01$; ††† $P < 0.001$. Same age groups different from diazepam: * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$ and from pethidine: § $P < 0.02$; §§ $P < 0.01$. Moderate = small fine movements in face, neck, fingers and trunk; violent = vigorous movements in extremities*

Premedicant	Restless falling asleep	Frequency of apnoea (%)	Eyelash reflex present	Eye movements present	Fasciculations after suxamethonium: None	Moderate	Violent
Pethidine 1.0 mg kg^{-1}							
Less than 5 yr (17)	41	71	0	0	21	50	29
Older than 5 yr (32)	3††	94	0	9	8	40	52
Diazepam 0.25 mg kg^{-1}							
Less than 5 yr (20)	55	90	0	0	18	53	29
Older than 5 yr (26)	8†††	77	8	12	0	32	68†
Flunitrazepam 0.02 mg kg^{-1}							
Less than 5 yr (20)	25*	80	0	0	21	50	24
Older than 5 yr (30)	0†	83	0	0	3	75**§	17***§§

than in the older children (0–8%). In the younger children flunitrazepam was associated with a more peaceful induction of anaesthesia than was diazepam. The frequency of apnoea ranged from 71 to 90% in different groups and eyelash reflex and eye movements almost always disappeared. The fasciculations following suxamethonium were more violent in the older children premedicated with pethidine and diazepam than in those premedicated with flunitrazepam.

Immediately after injection, thiopentone decreased arterial systolic pressure from 12 to 24 mm Hg in different groups (fig. 2). This decrease was significantly greater in the younger children premedicated with diazepam and flunitrazepam than in the older children premedicated with these drugs. After tracheal intubation, the increase in systolic pressure ranged from 20 to 45 mm Hg in different groups. In the younger children this increase was more pronounced in association with flunitrazepam than with pethidine.

At 2 and 24 h after anaesthesia, 10–33% of the children older than 5 yr did not recall the pictures (table V). There were no statistically significant differences between the groups. Only 14 of 57 children less than 5 yr co-operated in the assessment of amnesia and the results from these children were excluded.

At 45±13 min after injection, the serum concentration of diazepam was similar in both age groups whereas 90 min after injection, it had decreased in the younger children but increased in the older ones (table VI). All concentrations of flunitrazepam were significantly greater in the older than in the younger children and in both age groups the decrease was time-dependent.

TABLE V. *Percentages of children older than 5 yr of age not recalling the pictures shown to them immediately before the start of anaesthesia. Number of children in parentheses*

Premedicant	Not recalling the pictures when asked after anaesthesia	
	2 h	24 h
Pethidine 1.0 mg kg^{-1} (25)	22%	11%
Diazepam 0.25 mg kg^{-1} (20)	10%	10%
Flunitrazepam 0.02 mg kg^{-1} (20)	33%	33%

TABLE VI. *Concentrations of diazepam and flunitrazepam in serum (mean values ± SEM) 45 ± 13 (SD) and 90 min after their i.m. injection. Number of children in parentheses. Significant differences: from children less than 5 yr = †$P < 0.001$; from the value at 90 min = *$P < 0.01$*

Premedicant	Concn in serum (ng ml^{-1})	
	45 ± 13 min	90 min
Diazepam 0.25 mg kg^{-1}		
Less than 5 yr (19)	137 ± 23	114 ± 14
Older than 5 yr (21)	133 ± 34	152 ± 31
Flunitrazepam 0.02 mg kg^{-1}		
Less than 5 yr (19)	3.1 ± 0.42	2.5 ± 0.47
Older than 5 yr (29)	7.2 ± 0.90†*	5.6 ± 0.40†

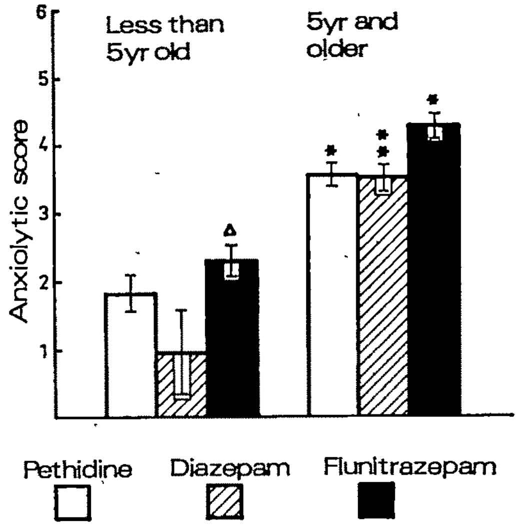

FIG. 1. Anxiolysis score in different treatment groups immediately before the start of anaesthesia. The anxiolytic effect was classified as poor when the score was 0–1, fair 2–3, good 4–5 and excellent 6–7. Bars indicate SEM. Mean values ± SEM from 19–29 children. Significant difference from the corresponding groups of children less than 5 yr of age: *$P < 0.01$, **$P < 0.001$. Significant difference from diazepam in the children less than 5 yr of age: Δ = $P < 0.05$.

DISCUSSION

Both flunitrazepam and pethidine had an anxiolytic effect in the children less than 5 yr, whereas the effect of diazepam was not satisfactory. All the premedicants studied produced a good anxiolytic effect in the children of more than 5 yr. Furthermore, a good anxiolytic effect seemed to be associated with a peaceful induction of anaesthesia.

Anxiolytic effect

Diazepam 0.25 mg kg^{-1} and flunitrazepam 0.02 mg kg^{-1} had an equipotent anxiolytic effect in children of 5 yr and more. Dundee, Vandarajan and others (1976) and Korttila and others (1978) found that in the same dose ratio (1 : 12.5) as was used in the present study, diazepam and flunitrazepam were equipotent sedatives in adults. Kammer and others (1975), however, found that flunitrazepam 2 mg had an anxiolytic effect when used for i.m. premedication in adult patients whereas diazepam 10 mg was without effect in the same (experimental) conditions. The discrepancy between the comparative studies of diazepam and flunitrazepam may be the result of the different dose ratios of the drugs, 1 : 12.5 and 1 : 5, used in the different studies.

In the younger children flunitrazepam produced a significantly better anxiolytic effect than did diazepam. Both benzodiazepines had a better anxiolytic effect in the older compared with younger children. There may be several reasons for the differences between the two groups. Because of uncontrollable fearful reactions, younger children may need greater sedation than the older ones. Furthermore, the smaller concentration of flunitrazepam in the serum of the younger children may partly explain its poorer effect in these children. However, the differences in the action of diazepam cannot be explained on these grounds since there were no significant differences in serum concentrations. In addition, it has been found that the absorption of diazepam is better from the intestinal tract than from the muscle (Assaf, Dundee and Gamble, 1975). Therefore diazepam may cause a better anxiolytic effect given orally than given i.m. In neither group did pethidine differ significantly from

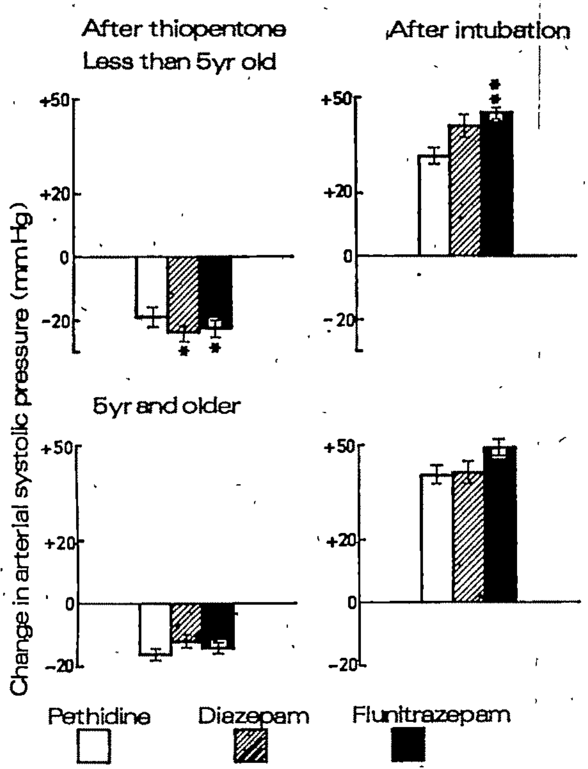

FIG. 2. Changes in arterial systolic pressure immediately after injection of thiopentone and 30 s after tracheal intubation. Bars indicate SEM. In different groups the mean initial values for arterial systolic pressures ranged from 114 to 128 mm Hg. Significant difference from the corresponding group of children older than 5 yr: $*P < 0.01$. Significant difference from pethidine in the children less than 5 yr: $**P < 0.001$.

the benzodiazepines, although its average effect in the younger children was better than that of diazepam. This finding is in agreement with the results of Bush (1968) who preferred pethidine to diazepam as premedication for children. Like the benzodiazepines, pethidine had a markedly better anxiolytic effect in the older children.

Induction characteristics

In all premedicant groups, falling asleep after thiopentone was more peaceful in older than in younger children. Flunitrazepam in the younger children produced a more tranquil induction than did diazepam. On the basis of the disappearance of eyelash reflex and eye movements, however, thiopentone 5 mg kg^{-1} produced the same level of anaesthesia in all groups.

In the older children, fasciculations caused by suxamethonium were less frequent after flunitrazepam than after diazepam or pethidine, whereas in the younger children there were no such differences. In the diazepam group the fasciculations were more violent in the older children. The preventive effect of benzodiazepines on these fasciculations may be the result of muscle relaxation of central origin caused by these drugs (Haefely et al., 1975).

Cardiovascular responses

After pethidine premedication, the cardiovascular responses following injection of thiopentone and tracheal intubation were similar to those in earlier reports of the same conditions (Saarnivaara, 1977). With the exception of flunitrazepam in the older children after intubation, the benzodiazepines did not differ from pethidine. However, the decrease in arterial systolic pressure following thiopentone was more pronounced in the younger children who received benzodiazepines.

Amnesic effects

In comparable sedative doses, flunitrazepam has a better and more prolonged amnesic action than diazepam in adult volunteers (Korttila and Linnoila, 1975, 1976) and in adult patients (Dundee and George, 1976; Dundee, George et al., 1976; Korttila et al., 1976). In the present study flunitrazepam also caused anterograde amnesia more often than did diazepam in the children older than 5 yr although the difference was not statistically significant. Pethidine had an amnesic effect in 22% and 11% of the children when studied 2 and 24 h after injection. This result agrees with that obtained by Dundee and Pandit (1972), who found that pethidine 50 mg produced amnesia in 20% of the adult patients. This result did not differ from that with placebo. In the present study pethidine did not differ from diazepam, which caused amnesia in 10% of the children. Dundee and Pandit (1972), however, found diazepam 10 mg given i.v. caused amnesia in 50% of the patients. This difference may be a result of the different modes of administration or different pharmacokinetics of diazepam in children and adults. The result may also show that children do not develop amnesia after diazepam so readily as do adults.

Drug concentrations in serum

Our results in children of different age groups confirm the earlier results in adults indicating that the pharmacokinetics of diazepam (Klotz et al., 1975) and of flunitrazepam (Korttila and Linnoila, 1976; Korttila et al., 1978) are age-dependent.

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COMPARAISON DE LA PETHIDINE, DU DIAZEPAM ET DU FLUNITRAZEPAM ADMINISTRES EN TANT QUE PREMEDICATION PAR VOIE INTRAMUSCULAIRE A DES ENFANTS DEVANT SUBIR UNE OPERATION OTO-RHINO-LARYNGOLOGIQUE

RESUME

La péthidine, à raison de 1 mg kg^{-1}; le diazépam, à raison de 0,25 mg kg^{-1} et le flunitrazépam, à raison de 0,02 mg kg^{-1} administrés par voie intramusculaire ont été comparés en tant que prémédications, au cours d'une étude à double inconnue effectuée sur 145 enfants devant subir une opération oto-rhino-laryngologique. Le flunitrazépam tout comme la péthidine ont eu un effet anxiolytique sur les enfants de moins de 5 ans, alors que le diazépam n'a eu que peu d'effet. Tous les médicaments ont été anxiolytiques sur les enfants âgés de 5 ans et plus. Le sommeil qui a suivi le thiopentone a été plus souvent agités chez les plus jeunes enfants que chez les plus âgés. Les réactions cardiovasculaires au thiopentone et à l'intubation trachéale ont été plus évidentes après l'administration de benzodiazépines aux enfants de moins de 5 ans. Après l'anesthésie, entre 10 et 33% des enfants les plus âgés ne se sont pas souvenus des images qui leur avaient été montrées avant l'anesthésie. Quarante-cinq minutes après l'injection (écart type ± 13 min), la concentration de diazépam dans le sérum a été similaire dans les deux groupes d'âge. Après 90 min, elle a diminué dans le groupe des plus jeunes, mais a augmenté chez les enfants les plus âgés. Toutes les concentrations de flunitrazépam ont été nettement plus importantes chez les enfants les plus âgés que chez les enfants les plus jeunes.

VERGLEICH VON INTRAMUSKULÄREM PETHIDIN, DIAZEPAM UND FLUNITRAZEPAM ALS VORBEHANDLUNGSMITTEL BEI SICH OTOLARYNGOLOGISCHER CHIRURGIE UNTERZIEHENDEN KINDERN

ZUSAMMENFASSUNG

Dosierungen von 1 mg/kg Pethidin, 0,25 mg/kg Diazepam und 0,02 mg/kg Flunitrazepam wurden in einer Doppel-

blindstudie als Vorbehandlungsmittel bei 145, sich otolaryngologischer Chirurgie unterziehenden Kindern verglichen. Sowohl Flunitrazepam als auch Pethidin hatten auf unter 5 Jahre alte Kinder eine anxiolytische Wirkung, während die Wirkung von Diazepam geringfügig war. Alle Drogen wirkten anxiolytisch bei Kindern im Alter von 5 Jahren und älter. Auf Thiopenton folgender Schlaf war bei den jüngeren Kindern häufiger unruhig, als bei den älteren. Kreislaufreaktionen auf Thiopenton und auf Trachealintubation waren bei unter 5 Jahre alten Kindern am augenscheinlichsten nach Benzodiazepinen. Nach der Narkose konnten sich 10–33% der älteren Kinder nicht an ihnen vor der Narkose gezeigte Bilder erinnern. Fünfundvierzig (±13) Minuten nach Injektion war die Diazepamkonzentration in Serum in beiden Altersgruppen gleich, nach 90 Min nahm sie in den jüngeren Kindern ab und in den älteren Kindern zu. Alle Flunitrazepamkonzentrationen waren bei den älteren Kindern im Vergleich mit den jüngeren Kindern bedeutend höher.

COMPARACION ENTRE PETIDINA, DIAZEPAM Y FLUNITRAZEPAM I.M. COMO PREMEDICAMENTOS EN NINOS SOMETIDOS A CIRUGIA OTOLARINGOLOGICA

SUMARIO

Se compararon petidina 1 mg kg^{-1}, diazepam 0,25 mg kg^{-1} y flunitrazepam 0,02 mg kg^{-1} i.m. como premedicamentos en un estudio de doble anonimato conducido con 145 niños sometidos a cirugía otolaringológica. Tanto el flunitrazepam como la petidina ejercieron un efecto ansiolítico sobre los niños menores de 5 años, mientras que el diazepam surtió poco efecto. Todas las drogas resultaron ansiolíticas en los niños de 5 años y mayores. El sueño que siguió la administración de tiopentona fue más a menudo inquieto en los niños menores que en los mayores. Las respuestas cardiovasculares a la tiopentona y a la intubación traqueal fueron más notables tras la administración de benzodiazepinas en niños menores de 5 años. Después de la anestesia, 10–33% de los niños mayores no pudieron recordar las ilustraciones que les fueron mostradas antes de la anestesia. Cuarenticinco (±SD 13) minutos después de la inyección, la concentración de diazepam en el suero fue semejante en ambos grupos de edades; al cabo de 90 min disminuyó en los niños menores y aumentó en los mayores. Todas las concentraciones de flunitrazepam fueron significativamente superiores en los niños mayores en comparación con los menores.

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COMPARISON OF DIAZEPAM AND FLUNITRAZEPAM AS ADJUNCTS TO GENERAL ANAESTHESIA IN PREVENTING AROUSAL FOLLOWING SURGICAL STIMULI

M. A. K. MATTILA, K. SÄILÄ, T. KOKKO AND T. KÄRKKÄINEN

SUMMARY

A comparison has been made between the effects of the administration of flunitrazepam 1 mg i.v. and diazepam 10 mg i.v. in 90 female patients undergoing abdominal surgery. The drugs were given immediately before the skin incision as a booster to the induction agent thiopentone. The response to the incision, the quality of anaesthesia and the need for supplementary medication during maintenance were monitored. A standard post-anaesthesia interview was performed to evaluate the amnesic action and patient acceptability. The skin incision caused only slight increases in arterial pressure and heart rate in both groups. Only six patients of the diazepam group reacted to the incision with defensive movements. The overall quality of anaesthesia was better ($P < 0.05$) and the need for supplementary doses of pethidine lower ($P < 0.01$) in the flunitrazepam group. Recovery was equally good and the duration of sleep after operation was the same in both groups. The frequency of nausea after operation was low. The post-anaesthesia interview revealed that flunitrazepam possesses a more specific anterograde amnesic action than diazepam. Acceptability of the anaesthesia to the patient was equally good in both groups.

In classical "balanced" anaesthesia the effects of premedication agents, induction agents, analgesic drugs and neuromuscular blocking agents are combined with those of the inhalation anaesthetics to produce clinical anaesthesia. However, there are reports in the literature which have claimed that, under such a technique, the patient may be aware during the operation and be unable to communicate this fact (Hutchinson, 1961; Wilson and Turner, 1969; Scott, 1972; Abouleish and Taylor, 1976). The frequency of such awareness may be assessed by interviewing the patients, after recovery, regarding their recall of the operation (Taub and Eisenberg, 1975; Wilson, Vaughan and Stephen, 1975; Agarwal and Sikh, 1977).

It is likely that the most severe stimulus occurring during the operation is the initial skin incision and patients often react to this stimulus with defensive movements or facial expressions. Awareness may be present also (Eisele, Weinreich and Bartle, 1976). In addition the heart rate and arterial pressure increase markedly at this moment (Cullen et al., 1972; Tantisira and McKenzie, 1974; Vaughan, Cobb and Roa, 197[illegible]). During the maintenance of anaesthesia the surgical stimuli vary in intensity. There may be sudden pain as a result of traction or at the closure of the wound. These cause arousal symptoms unless anaesthesia is sufficiently deep (Johnstone, 1972).

We have observed a need to deepen anaesthesia on skin incision and to achieve this we have used an additional dose of a hypnotic drug given immediately before the skin incision. The choice of drug is not always easy. It should be effective, sufficiently long-acting and, in view of the possibility of arousal during the operation, should have an amnesic action. In addition, it should be without local and general side-effects.

The drugs which seem to fulfil these requirements best are certain derivatives of the benzodiazepines. Flunitrazepam (Rohypnol, F. Hoffmann-La Roche & Co., Basle) has been studied widely as an induction agent in anaesthesia (De Oliveira et al., 1973; Dundee, Vendarajan et al., 1976; Clarke and Lyons, 1977; [illegible], 1977). It is related chemically to diazepam, which has a well-established place in anaesthesia. The clinical profile of flunitrazepam resembles that of diazepam, both having a slow onset of action and showing considerable individual variation in response. As induction agents they are long-acting and the effects on the circulation and respiration are minimal (Stovner, Endresen and Österud,

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1973; Trieger, 1973; Yoo, 1973). However, according to Stovner, Endresen and Österud (1973), flunitrazepam has a more specific hypnotic effect than diazepam. In addition, it may possess a better amnesic action (Korttila and Linnoila, 1976; Korttila et al., 1978), although in other studies (Dundee, George et al., 1976; George and Dundee, 1977) no difference was observed between flunitrazepam and diazepam.

Thus we decided to investigate the use of such administration in the prevention of arousal, comparing diazepam and flunitrazepam in a controlled randomized trial.

METHODS

Ninety female patients undergoing gynaecological or abdominal surgery were studied. Poor-risk patients were excluded. The patients were anaesthetized by the same anaesthetist using a standard technique. One to two hours before operation scopomorphine (scopolamine 0.6 mg ml^{-1}; morphine 20 mg ml^{-1}) was administered i.m. The average dose was 0.008 ml kg^{-1}. Immediately before the induction of anaesthesia, atropine 0.01 mg kg^{-1} was given i.v. A rapidly flowing solution of 0.3% sodium chloride in 5% dextrose acted as a carrier for the i.v. injections. Induction was with thiopentone, given as a slow i.v. injection into a peripheral vein until the eyelid reflex was abolished totally. The average dose was 5 mg kg^{-1}. Thereafter suxamethonium 1 mg kg^{-1} was given to facilitate tracheal intubation. Neuromuscular blockade was maintained with alcuronium (about 0.2 mg kg^{-1}) and analgesia with pethidine (approx. 0.5 mg kg^{-1}). In 11 patients an infusion of suxamethonium was used in place of alcuronium. About 2 min before the skin incision the patients were given a single i.v. dose of coded solution containing either diazepam 10 mg or flunitrazepam 1 mg.

Ventilation of the lungs was controlled either manually or mechanically using a mixture of nitrous oxide in oxygen (2 : 1) via a semi-closed circuit at a frequency of 12 b.p.m. Pa_{CO_2} was maintained close to normal values. During the maintenance of anaesthesia, analgesia and neuromuscular blockade were maintained with supplementary doses of pethidine 10 mg and alcuronium 2.5 mg given as required. If any symptoms of arousal appeared supplementary doses of thiopentone 50 mg were given. At the end of the operation the effect of alcuronium was antagonized with neostigmine 2 mg preceded by atropine 1 mg. Extubation was performed when adequate spontaneous ventilation had returned. The quality of anaesthesia, the patient's symptoms and the start of spontaneous respiration were evaluated by the anaesthetist according to a standard plan. Arterial pressure and heart rate were recorded routinely and at five fixed points: before induction, immediately after intubation, before and 1 min after the administration of the coded drug and 1 min after the incision.

TABLE I. *The form for post-anaesthetic interview*

Do you recall	Yes, clearly	Yes, unsure	No	No opinion
1. the administration of the premedication?				
2. the transfer to the operating theatre?				
3. the transfer onto the operating table?				
4. the intravenous injection?				
5. falling asleep?				
6. the transfer from the operating table?				
7. awakening in the recovery room?				
8. the transfer to the ward?				
9. Do you have memories of the actual operation?				
10. Did you have nausea in the recovery room?				
11. Did you receive analgesics in the recovery room?				

Your overall opinion of the anaesthetic? very pleasant, pleasant, no comment, unsatisfactory, bad

Your overall opinion of the recovery? very pleasant, pleasant, no comment, unsatisfactory, bad

Would you like a similar anaesthetic in future, if necessary? definitely yes, yes, no opinion, not necessarily, absolutely not

Did you have nausea? not at all, slightly, yes, severe nausea, very severe nausea and vomiting

The effect of the analgesic was: very good, good, moderate, poor, very poor

The patient was allowed to wake spontaneously in the recovery room without any active stimulation. The duration of sleep before spontaneous awakening, the patient's behaviour, the occurrence of nausea and pain after consciousness had been regained and the opinion of the recovery room nurses about the awakening were all recorded. The amounts of anti-emetic medication and analgesic drugs given in the recovery room were noted. Analgesic drugs were given only if the patient requested them for the relief of pain, and the time of administration was recorded. The patient was moved to the ward when fully awake and this time was noted.

On the day following operation the patients were interviewed and their opinions of the anaesthesia and recovery obtained by two anaesthetic nurses using a standard questionnaire (table I).

Statistical analysis of the results was performed using Student's paired *t* test or the Chi-square test.

RESULTS

Anaesthesia

The patients in the diazepam and flunitrazepam groups were fully comparable in terms of number, sex, age, weight and height (table II) although the duration of surgery was longer in the flunitrazepam group ($P < 0.05$) (table II).

Scopomorphine 0.008 ml kg^{-1} was given to both groups and there were no differences between the

TABLE II. *Characteristics of the patients, the duration of premedication before operation and the duration of operation in the diazepam and flunitrazepam groups. The values are mean ± SEM. Values of* P *derived by* t *test*

	Diazepam	Flunitrazepam	*P*
Number of patients	45	45	
Age (yr)	35.5 ± 1.6	37.5 ± 1.2	n.s.
Weight (kg)	61.8 ± 1.3	62.5 ± 1.4	n.s.
Height (cm)	161.0 ± 0.9	161.7 ± 0.8	n.s.
Duration of operation (min)	76.6 ± 3.3	90.7 ± 4.3	0.05
Duration of premedication (min)	90.6 ± 5.3	86.6 ± 3.6	n.s.

TABLE III. *The effect of premedication and quality of induction in the flunitrazepam and diazepam groups. The values are numbers of patients*

	Diazepam	Flunitrazepam
Premedication		
good	39	39
moderate	5	5
poor	1	1
total	45	45
Induction		
good	31	32
moderate	10	13
poor	4	0
total	45	45

TABLE IV. *The quality of anaesthesia during maintenance and at the end of anaesthesia and the start of spontaneous respiration in the diazepam and flunitrazepam groups. The values are numbers of patients. Values of* P *derived by Chi-square test*

	Diazepam		Flunitrazepam		*P*
Maintenance of anaesthesia					
excellent (no reactions to surgical stimuli)	10	27	21	36	< 0.05
good	17		15		
moderate (patient reacts to stimuli with movements)	9		7		
poor (defensive reactions, e.g. movements of limbs)	5	9	2	2	< 0.05
very poor (marked defensive reactions interfering with surgical procedure)	4		0		
total	45		45		
Start of spontaneous respiration					
excellent	14	27	20	33	n.s.
good	13		13		
moderate	10		7		
poor	7	8	5	5	n.s.
very poor	1		0		
total	45		45		

groups in the effect of this premedication or of the quality of induction with thiopentone (table III).

At the moment of skin incision movements were observed in six patients of the diazepam group. In the flunitrazepam group, no reactions to incision were seen. Table IV shows the differences in the quality of the maintenance of anaesthesia and the start of spontaneous breathing. A score of "excellent" or "good" was given 36 times in the flunitrazepam group and 27 times in the diazepam group for the maintenance of anaesthesia. Scores of "poor" or "very poor" were given twice in the flunitrazepam group and seven times in the diazepam group ($P < 0.05$). The start of spontaneous respiration was excellent or good 33 times in the flunitrazepam group and 27 times in the diazepam group. The low scores, "poor" and "very poor", were given five times in the flunitrazepam group and eight times in the diazepam group. This difference was not statistically significant.

Table V shows that the need for pethidine was significantly less ($P < 0.01$) in the flunitrazepam group compared with the diazepam group, but there was no difference in the amount of alcuronium required.

TABLE V. *The use of pethidine (mg kg^{-1} h^{-1}) and alcuronium (mg kg^{-1} h^{-1}) during maintenance of anaesthesia in the diazepam and flunitrazepam groups. Values are mean ± SEM. Values of* P *derived by* t *test*

	Diazepam	Flunitrazepam	*P*
Pethidine	0.71 ± 0.04	0.58 ± 0.02	< 0.01
(*n*)	(45)	(45)	
Alcuronium	0.20 ± 0.01	0.19 ± 0.01	n.s.
(*n*)	(36)	(43)	

During the maintenance of anaesthesia one to three 50-mg supplementary doses of thiopentone were required by 26 patients in the diazepam group and by 21 patients in the flunitrazepam group. This difference was not statistically significant.

Figures 1 and 2 show the arterial systolic and diastolic pressures and the heart rates noted at intervals during anaesthesia. There was an almost identical pattern of cardiovascular reaction in both groups following the administration of the coded drug. Although the arterial diastolic pressure increased significantly ($P < 0.05$) following the skin incision in both groups, overall there were hardly any responses attributable to the skin incision.

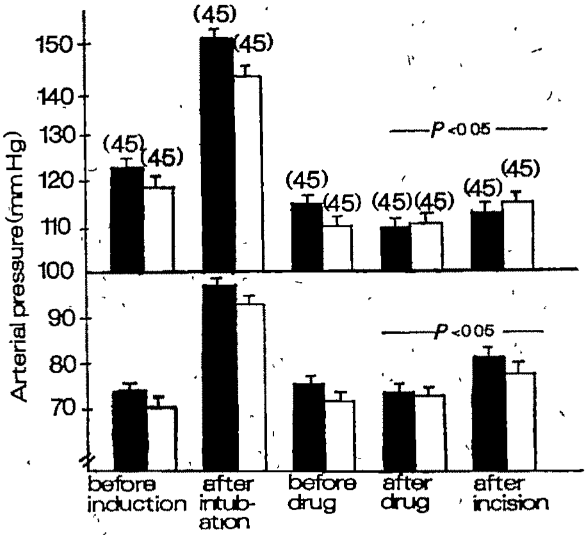

FIG. 1. Arterial systolic (top) and diastolic (bottom) pressure in the diazepam (black) and flunitrazepam (white) groups. The columns represent mean ± SEM. Number of patients in parentheses. Drug = diazepam or flunitrazepam.

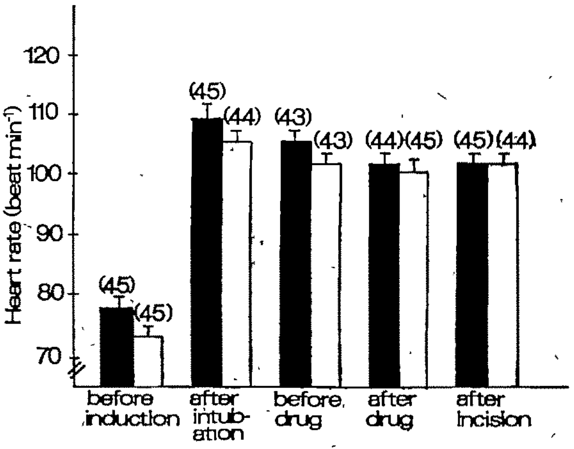

FIG. 2. Heart rate in the diazepam (black) and flunitrazepam (white) groups. The columns represent mean ± SEM. Number of patients in parentheses. Drug = diazepam or flunitrazepam.

Recovery

There were no differences between the flunitrazepam and diazepam groups in the duration of sleep after arrival in the recovery room or the duration of stay in the recovery room before transfer to the ward (table VI).

The behaviour of the patient upon wakening and the opinion of the nursing staff of the condition of the patient are shown in table VII. There were no statistically significant differences between the two groups.

In the recovery room slight nausea was reported in 12 patients and moderate nausea in three patients in the flunitrazepam group. There was no vomiting after operation in this group. In the diazepam group nausea and vomiting were observed in one patient, moderate nausea in five and slight nausea in six. An antiemetic drug was given to five patients in each group during the recovery period. In the flunitrazepam group 25 patients received an analgesic drug at an average of 2 h 44 min after operation and 26 of the diazepam group at an average of 3 h 13 min after operation. This difference was not statistically significant.

TABLE VI. *The duration of sleep (min) in the recovery room before spontaneous awakening and the time (min) spent in the recovery room in the diazepam and flunitrazepam groups. The values are mean ± SEM. Values of* P *derived by* t *test*

	Diazepam	Flunitrazepam	*P*
Duration of sleep	80.59 ± 7.56	83.11 ± 7.40	n.s.
Time in recovery	240.09 ± 13.46	229.15 ± 11.52	n.s.

Patient interview

Table VIII shows the differences in the recall of the operation and in recovery between the flunitrazepam and diazepam groups. One patient in the

TABLE VII. *The patients' behaviour and condition on awakening as scored by the nursing staff in the diazepam and flunitrazepam groups. The values are numbers of patients. Values of* P *derived by Chi-square test*

	Diazepam	Flunitrazepam	*P*
Behaviour of patients on awakening			
good (calm and quiet, quick recovery of consciousness)	39	34	n.s.
moderate (slight disorientation and anxiety or excitement)	5	11	
poor (excitement or anxiety on awakening, difficulties in regaining consciousness)	0	0	
no score	1	0	
total	45	45	
Opinion of the nursing staff of patients' condition during recovery observation			
good	35	32	n.s.
moderate	8	12	
poor	0	0	
no score given	2	1	
total	45	45	

TABLE VIII. *Answers to the post-anaesthesia questionnaire. The values are numbers of patients*

	Diazepam ($n = 45$)	Flunitrazepam ($n = 45$)	*P*
Remembered			
receiving premedication	45	45	
transfer to operating theatre	45	45	
transfer to operating table	44	45	
insertion of i.v. needle	42	43	
falling asleep	14	11	
operation	0	1	
transfer to recovery room	0	0	
awakening	34	32	
feeling of nausea	9	7	
mistakes	7	12	n.s.
administration of analgesic	10	6	
mistakes	17	22	n.s.
transfer to ward	30	35	

flunitrazepam group recalled events during the operation and experienced these as unpleasant.

Twelve patients in the flunitrazepam group and seven of the diazepam group made mistakes in remembering the occurrence of nausea in the recovery room. The administration of an analgesic was remembered incorrectly 22 times in the flunitrazepam group and 17 times in the diazepam group. There were no statistically significant differences in these figures between the two groups.

Thirty-nine patients in the flunitrazepam group and 42 of the diazepam group experienced anaesthesia and recovery as pleasant. Three patients in the flunitrazepam group and two in the diazepam group mentioned that postoperative nausea and pain was the reason for discomfort in the recovery room. The figures do not differ significantly between the two groups (table IX).

TABLE IX. *The patients' opinions of anaesthesia and recovery according to post-anaesthesia interview in the diazepam and flunitrazepam groups. The values are numbers of patients. Values of* P *derived by Chi-square test*

	Diazepam	Flunitrazepam	*P*
Anaesthesia			
pleasant	42	39	n.s.
uncomfortable	3	5	
unpleasant	0	1	
total	45	45	
Recovery			
pleasant	30	32	n.s.
uncomfortable	12	7	
unpleasant because of pain and nausea	2	3	
unpleasant for other reasons	1	3	
total	45	45	

DISCUSSION

Awareness during operation can be a terrible experience for the patient, and may lead to nightmares and psychoses (Levinson, 1965; Bergström and Bernstein, 1968; Brice, Hetherington and Utting, 1970; Scott, 1972; Blacher, 1975; Wilson, Vaughan and Stephen, 1975). It may remain unknown to the anaesthetic staff unless patients are interviewed systematically following anaesthesia.

Muscle relaxation for surgery may prevent the appearance of the patient's normal defence mechanisms. However, by using lighter premedication, by decreasing the amount of inhalation anaesthesia and by changing from hyperventilation to normoventilation, the possibility of awareness during anaesthesia may be increased. "Lighter" anaesthesia often requires supplementation in the form of hypnotic drugs. Supplementary drugs are given currently to the patient only when the first symptoms of arousal appear. However, at this moment the patient may be awake and may remember the events later. In addition to small defensive movements, lacrimation, sweating and facial expressions, reactions can be seen also as an increase in arterial pressure and heart rate. At the moment of skin incision, especially, marked increase of arterial pressure and heart rate are often observed. It seems logical that anaesthesia should be deepened immediately before the skin incision. Our experience has shown that this can be achieved by giving a booster dose of an hypnotic (Mattila, Martikainen and Säilä, 1977). Previously, we have used thiobarbiturates for this purpose, but the benzodiazepine derivatives can be regarded as superior because of their established amnesic effects (Clarke et al., 1970; Dundee and Pandit, 1972; Gregg, Ryan and Levin, 1974; Thornton and Martin, 1976; George and Dundee, 1977; Korttila et al., 1978). The efficacy of the drug can be evaluated during anaesthesia by observing the patient's reactions, arterial pressure and heart rate, but its effects on subjective experience of anaesthesia can be evaluated only by a systematic interview following anaesthesia.

In our study six patients of the diazepam group and none of the flunitrazepam group reacted to the skin incision with symptoms of arousal.

There was a significant difference in favour of flunitrazepam regarding the overall quality of anaesthesia. The scores for both groups were predominantly excellent or good.

The start of spontaneous respiration at the end of anaesthesia depends on the carbon dioxide concentration and reflects the depressant effect on respiration of the anaesthetic agents given. This criterion was usually scored "good" or "excellent" and there was no difference between the two groups. The benzodiazepines have little effect on respiration (Stovner and Endresen, 1965; Freuchen, Østergaard and Ohrt Mikkelsen, 1976). Because supplementary doses of pethidine and thiopentone were given to patients only when arousal symptoms were present, the difference ($P<0.01$) in favour of flunitrazepam suggests a more specific action as a hypnotic. The same amount of myoneural blocker was used in both groups.

Normally, when the patient is being prepared for surgery there are few stimuli present and this results in a progressive decrease in arterial pressure. The skin incision causes a sudden increase in arterial pressure and heart rate. In this series both diazepam and flunitrazepam abolished this response almost completely. Another reason for using diazepam or flunitrazepam in conjunction with analgesics is to achieve and maintain sufficiently deep anaesthesia. Maintenance of anaesthesia was evaluated as "excellent" or "good" in the great majority of patients, especially when flunitrazepam was given. The significant difference ($P < 0.01$) in the need for pethidine during anaesthesia suggested a superior influence of flunitrazepam on the quality of anaesthesia.

There were no differences between the two groups in the duration of sleep until spontaneous awakening or the duration of stay in the recovery room. The patients stayed in the recovery room for up to 6 h until they had recovered totally. Recovery was calm and quiet in 39 patients in the diazepam group and in 34 of the flunitrazepam group. There was no excitement or anxiety on awakening in either group. Thus, deepening the level of anaesthesia does not impair recovery.

In both groups the frequency of nausea after operation was surprisingly small considering that the patients were women undergoing abdominal surgery. Janhunen and Tammisto (1972) noted up to 65% frequency of vomiting after cholecystectomy in women. Our results seemed to confirm earlier findings indicating that the benzodiazepine derivatives have antiemetic properties (Dundee and Haslett, 1970; Mattila, Rajpar and Pystynen, 1974; Mattila, Martikainen and Säilä, 1977).

The results of the post-anaesthesia interview suggested that both drugs tested have an amnesic action. The patients recalled events until insertion of the i.v. needle. The number of mistakes made in recalling post-anaesthesia events was greater in the flunitrazepam group, suggesting a greater degree of anterograde amnesia. Only one patient in the flunitrazepam group had some memories of the actual operation and experienced this as unpleasant. This particular individual had a similar experience during a previous anaesthetic. Thirty-nine patients in the flunitrazepam group and 42 in the diazepam group had a favourable opinion of the anaesthetic, which suggested that patient acceptability was satisfactory. Complaints referring to the post-anaesthetic period were mainly those of pain and nausea in the recovery room.

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COMPARAISON DU DIAZEPAM ET DU FLUNITRAZEPAM COMME AUXILIAIRES DE L'ANESTHESIE GENERALE POUR PREVENIR LE REVEIL APRES STIMULATION CHIRURGICALE

RESUME

On a fait une comparaison entre les effets de l'administration de flunitrazépam, à raison de 1 mg par voie intraveineuse, et de diazépam, à raison de 10 mg par voie intraveineuse, sur 90 femmes devant subir une intervention chirurgicale à l'abdomen. Les médicaments ont été administrés immédiatement avant l'incision de la peau pour renforcer le thiopentone, agent d'induction de l'anesthésie. On a surveillé la réaction à l'incision, la qualité de l'anesthésie et la nécessité d'avoir recours à des médicaments supplémentaires pendant l'entretien de l'anesthésie. On a procédé à une interview standard après l'anesthésie pour déterminer l'action amnésique et son acceptabilité par la malade. L'incision de la peau n'a causé que de légères augmentations de la pression artérielle et de la fréquence cardiaque dans les deux groupes. Seules six malades du groupe diazépam ont réagi à l'incision par des mouvements défensifs. La qualité d'ensemble de l'anesthésie a été meilleure ($P < 0{,}05$) et la nécessité d'utiliser des doses supplémentaires de péthidine a été plus faible ($P < 0{,}01$) dans le groupe flunitrazépam. La récupération a été aussi bonne dans un groupe que dans l'autre et la durée du sommeil après l'opération a été la même dans les deux groupes. La fréquence de nausées après l'opération a été faible. L'interview effectuée après l'anesthésie a révélé que le flunitrazépam possède une action amnésique antérograde plus spécifique que le diazépam. L'acceptabilité de l'anesthésie du point de vue du malade a été aussi bonne dans un groupe que dans l'autre.

VERGLEICH VON DIAZEPAM UND FLUNITRAZEPAM ALS HILFSMITTEL BEI VOLLNARKOSE IN DER VERHINDERUNG EINES ERWACHENS INFOLGE VON CHIRURGISCHEN STIMULI

ZUSAMMENFASSUNG

Es wurde ein Vergleich zwischen den Wirkungen angestellt, die die intravenöse Eingabe von 1 mg Flunitrazepam und 10 mg Diazepam in 90, sich Bauchchirurgie unterziehenden Patientinnen hatte. Die Drogen wurden unmittelbar vor dem Hautschnitt als Verstärker zum eigentlichen Induktionsmittel Thiopenton eingegeben. Es wurden die Reaktion auf den Einschnitt, die Qualität der Narkose und das Erfordernis für Zusatzmedikation während der Aufrechterhaltung der Narkose überwacht. Zur Bewertung der Amnesiewirkung und Annehmbarkeit der Drogen wurde mit den Patientinnen ein routinemässiges Interview durchgeführt. Der Hautschnitt verursachte nur geringfügige Anstiege im arteriellen Druck und in der Pulszahl bei beiden Gruppen. Aus der Diazepamgruppe reagierten nur sechs Patientinnen mit Abwehrbewegungen auf den Hautschnitt. Bei der Flunitrazepamgruppe war die allgemeine Narkosequalität besser ($P < 0{,}05$) und das Erfordernis für Zusatzdosen von Pethidin niedriger ($P < 0{,}01$). Bei beiden Gruppen war die Erholung gleich gut und fand

ohne Ängstlichkeit oder Aufregung statt und die postoperative Schlafdauer war gleich lang. Die Haufigkeit postoperativer Übelkeit war niedrig. Das Postnarkoseinterview zeigte, dass Flunitrazepam eine spezifischere vorgradige Amnesiewirkung besitzt, als Diazepam. Für die Patientinnen beider Gruppen war die Annehmbarkeit gleich gut.

COMPARACION ENTRE DIAZEPAM Y FLUNITRAZEPAM COMO ADICIONES A LA ANESTESIA GENERAL PARA EVITAR EL DESPERTAMIENTO TRAS EL ESTIMULO QUIRURGICO

SUMARIO

Se ha hecho una comparación entre los efectos de la administración de flunitrazepam 1 mg i.v. y diazepam 10 mg i.v. en 90 mujeres pacientes sometidas a cirugía abdominal. Las drogas fueron administradas inmediatamente antes de realizarse la incisión de la piel para reforzar el agente inductor, tiopentona. Se fiscalizó la respuesta a la incisión, la calidad de la anestesia y la necesidad de medicación suplementaria durante el mantenimiento. Se celebró una entrevista normal de postanestesia para evaluar la acción amnésica y aceptabilidad del paciente. La incisión en la piel causó sumentos solamente ligeros en la presión arterial y latidos del corazón de ambos grupos. Solamente seis pacientes en el grupo de diazepam reaccionaron a la incisión con movimientos defensivos. La calidad general de la anestesia fue superior ($P<0,05$) y la necesidad de dosis suplementarias de petidina fue inferior ($P<0,01$) en el grupo de flunitrazepam. La recuperación fue igualmente satisfactoria y la duración del sueño después de la operación fue igual en ambos grupos. La frecuencia de náusea después de la operación fue escasa. La entrevista postanestésica reveló que el flunitrazepam posee una acción amnésica anterograda más específica que el diazepam. La aceptabilidad de la anestesia de parte del paciente fue igualmente buena en ambos grupos.

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STUDIES OF DRUGS GIVEN BEFORE ANAESTHESIA
XVII: ANTICHOLINERGIC PREMEDICANTS

R. K. MIRAKHUR, J. W. DUNDEE AND J. D. R. CONNOLLY

SUMMARY

The effects of premedication with the anticholinergic drugs atropine, hyoscine and glycopyrronium when administered by oral and i.m. routes have been evaluated in patients undergoing minor surgery and compared with a placebo using a double-dummy double-blind technique. Although the mouths of those patients who received adequate doses of anticholinergic drugs were dry, subjectively and observed, as compared with those who received a placebo, the overall course of anaesthesia did not appear to be different. Of the three drugs atropine seemed to be absorbed best following oral administration. Equally effective oral and i.m. doses of atropine were considered to be 2.0 and 1.0 mg respectively; of hyoscine 1.0 and 0.25–0.5 mg. The appropriate dose of glycopyrronium was 0.2 mg i.m. The routine use of anticholinergic drugs in preanaesthetic medication in minor surgery appears to be unnecessary.

The anticholinergic drugs atropine and hyoscine have been used traditionally in premedication on account of their antisialogogue actions and their vagolytic effects (Norris, 1971). In addition to these uses, such drugs have been shown variously to have some antiemetic action (Clarke, Dundee and Love, 1965), to prevent the occurrence of laryngeal spasm (Dripps, 1944), to provide sedation and amnesia (hyoscine) (West and Papper, 1950) and to increase the tone of the cardiac sphincter (Clark and Riddoch, 1962). According to Wangeman and Hawk (1942), hyoscine counteracts the respiratory depression produced by morphine.

However, some of these attributes have been questioned by Robson and Welt (1959), Eckenhoff and Oech (1960) and Rosen (1960). The disadvantages of atropine and hyoscine include the unpredictable antisialogogue action of the former (Wyant and Dobkin, 1957) and the weak cardiac action of the latter (Griggs and Adriani, 1954). Both drugs can produce restlessness, excitement and visual difficulty. Moreover, contradictory opinions have been expressed regarding the usefulness of routine anticholinergic premedication (Kessell, 1974; Falick and Smiler, 1975; Leighton and Sanders, 1976). However, a recent survey conducted in the United Kingdom showed that more than 60% of anaesthetists prescribed anticholinergic premedicants routinely (Mirakhur et al., 1978). Thus, there is a need for a re-evaluation of such therapy. The present study is part of such an investigation.

The new anticholinergic agent glycopyrronium has been evaluated and compared with atropine and hyoscine. This drug has been shown to possess a potent antisialogogue action with minimal cardiovascular effects (Wyant and Kao, 1974; Mirakhur, Dundee and Jones, 1978). Another aim of the present study was to assess the effectiveness of the oral administration of anticholinergic drugs, since diazepam is known to be an effective oral premedicant. Hence, the three drugs were evaluated following oral administration and when given parenterally.

PATIENTS AND METHODS

The study was carried out in fit adult patients who were undergoing mainly minor gynaecological surgery or electroconvulsive therapy (e.c.t.). Their physical characteristics, the dosage of drugs and the routes of administration are given in table I. The patients were seen in the ward on the evening before operation and their informed consent was obtained for participating in a drug trial, but they were not told that the drugs were being assessed for their drying effect.

The following were measured before the administration of the premedication and at 20, 40, 60 and 90 min later in the ward: heart rate, counted from either wrist for 1 min; arterial pressure, measured by upper arm sphygmomanometry; oral temperature, using a clinical thermometer; pupillary size, measured

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TABLE I. *Doses of anticholinergic drugs and their routes of administration with average (± SEM) ages and weights of the patients in the different groups*

Drug	Dose (mg)	Route	Age (yr)	Weight (kg)
Atropine	0.5	i.m.	35 ± 2.8	63 ± 3.0
Atropine	1.0	i.m.	36 ± 2.5	59 ± 1.4
Atropine	2.0	i.m.	33 ± 2.5	58 ± 1.7
Atropine	0.5	oral	33 ± 2.7	60 ± 2.6
Atropine	1.0	oral	35 ± 2.7	58 ± 2.0
Atropine	2.0	oral	32 ± 2.6	63 ± 1.9
Hyoscine	0.25	i.m.	37 ± 3.1	66 ± 2.1
Hyoscine	0.5	i.m.	35 ± 2.0	60 ± 2.0
Hyoscine	1.0	i.m.	36 ± 2.2	62 ± 1.5
Hyoscine	0.25	oral	35 ± 2.7	59 ± 1.8
Hyoscine	0.5	oral	36 ± 2.3	57 ± 2.0
Hyoscine	1.0	oral	31 ± 2.5	57 ± 1.6
Glycopyrronium	0.1	i.m.	30 ± 2.3	60 ± 2.0
Glycopyrronium	0.2	i.m.	30 ± 1.5	63 ± 3.1
Glycopyrronium	0.4	i.m.	37 ± 2.7	64 ± 2.8
Glycopyrronium	2.0	oral	41 ± 3.1	61 ± 2.0
Glycopyrronium	4.0	oral	32 ± 2.2	59 ± 2.0
Glycopyrronium	8.0	oral	30 ± 2.4	61 ± 2.3
Placebo			33 ± 2.0	59 ± 2.1

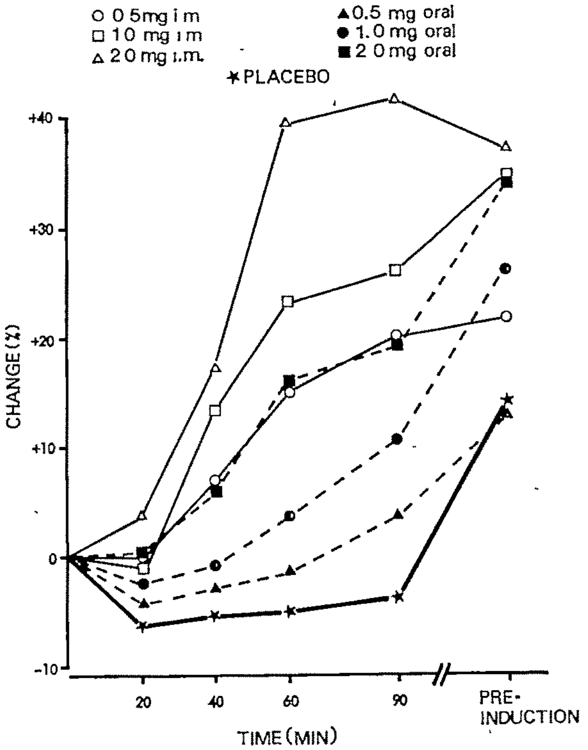

FIG. 1. Percentage changes in heart rate following administration of three doses of atropine by oral and i.m. routes.

using a transparent pupil gauge. At each time the patients were asked to classify the state of their mouth as dry, moderately dry or wet (moist). A note was made of any undesirable effects complained of by the patient or noted objectively.

The heart rate was recorded again before anaesthesia which was induced with thiopentone 4–6 mg kg^{-1} or methohexitone 1.5–1.8 mg kg^{-1}. Anaesthesia was maintained with 70% nitrous oxide in oxygen supplemented with further doses of barbiturate or an inhalation agent. Oxygen only was used in those patients undergoing e.c.t. If necessary, suxamethonium was used to produce neuromuscular blockade. An oropharyngeal airway was inserted routinely as a stimulus to salivation and endotracheal intubation was carried out in 13 (3.4%) patients. The anaesthetist examined the oropharynx for secretions and classified it as dry, moderately dry or wet. Heart rate was counted every 2 min during the course of anaesthesia. A note was made of coughing, hiccup, laryngospasm, cardiac arrhythmia and of the need for oropharyngeal suction.

There were 19 groups of 20 patients each (table I). The anticholinergic drugs were the sole premedication. A double-blind double-dummy scheme was employed in the administration of the drugs:

i. m. route	oral route
Active drug	Placebo
Placebo	Active drug
Placebo	Placebo

The results in each group were submitted to a paired *t* test and a Chi-square test was used to compare non-parametric observations.

RESULTS

The groups were broadly similar with respect to age and weight (table I) except that in those receiving glycopyrronium 2 mg orally the mean age was greater than in the other groups.

Heart rate

The baseline values were broadly similar in all groups (table II). The changes were most marked after atropine i.m., all doses producing a significant increase in heart rate ($P < 0.05 - < 0.001$) at 40, 60 and 90 min, heart rate having increased on an average by 26 and 42% following 1.0 and 2.0 mg respectively at 90 min. The oral administration of atropine 0.5 mg was virtually without effect except for a small but significant ($P<0.05$) decrease in rate at 20 min. However, the two larger doses caused significant tachycardia at 60–90 min. The effects of the two routes of administration of atropine are shown in figure 1.

Hyoscine administered by both routes produced minimal changes in heart rate although there was a significant ($P<0.05$) increase at 40, 60 and 90 min (fig. 2) following the administration of hyoscine 1 mg i.m.

The administration of glycopyrronium 0.1 mg i.m. caused a small decrease in heart rate; 0.2 mg produced no significant changes, while 0.4 mg produced a significant increase ($P<0.001$) at 60 and 90 min. The changes following oral glycopyrronium were minimal and mostly insignificant (table II, fig. 3).

The administration of the placebo produced no significant changes in heart rate throughout the 90 min of observation in the ward. However, in this and in most other groups heart rates had increased significantly just before the induction of anaesthesia.

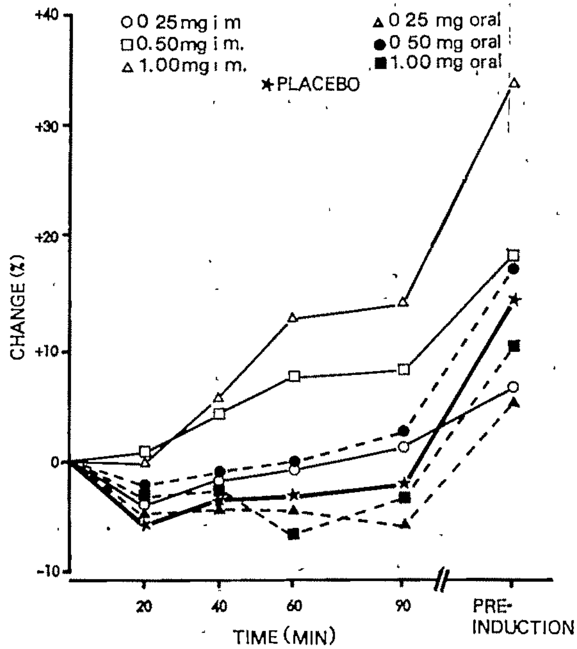

FIG. 2. Percentage changes in heart rate following administration of three doses of hyoscine by oral and i.m. routes.

Arterial pressure

The changes in systolic and diastolic pressures were minimal and are not reported in detail.

TABLE II. *Average heart rates ± SEM (beat* min^{-1}*) before and following premedication with the three anticholinergic drugs and placebo. (Statistical difference from the control value:* * $P<0.05$*;* ** $P<0.001$*)*

Drug	Dose (mg)	Route	Before drug	Time after administration (min) 20	40	60	90	Just before induction
Atropine	0.5	i.m.	74 ± 2.6	74 ± 2.3	79 ± 2.8*	86 ± 2.3**	90 ± 2.8**	93 ± 3.4**
Atropine	1.0	i.m.	74 ± 2.8	73 ± 2.8	84 ± 4.5*	91 ± 3.9**	93 ± 3.1**	100 ± 3.0**
Atropine	2.0	i.m.	79 ± 2.4	82 ± 2.5	93 ± 2.6**	110 ± 3.0**	113 ± 3.8**	109 ± 4.0**
Atropine	0.5	oral	73 ± 2.6	70 ± 2.4*	71 ± 2.2	72 ± 2.7	76 ± 2.8	83 ± 3.4*
Atropine	1.0	oral	78 ± 1.6	77 ± 1.3	77 ± 1.7	81 ± 2.1	86 ± 2.7*	99 ± 4.4**
Atropine	2.0	oral	76 ± 4.7	75 ± 2.3	80 ± 2.8	88 ± 4.0*	90 ± 3.6*	102 ± 4.7**
Hyoscine	0.25	i.m.	77 ± 2.5	75 ± 2.5	75 ± 2.6	76 ± 3.3	76 ± 2.8	82 ± 3.0
Hyoscine	0.5	i.m.	72 ± 2.3	72 ± 2.6	75 ± 3.4	78 ± 3.5	78 ± 3.6	85 ± 4.3*
Hyoscine	1.0	i.m.	75 ± 2.1	75 ± 2.0	79 ± 1.8*	85 ± 2.7*	86 ± 3.3*	101 ± 4.1**
Hyoscine	0.25	oral	80 ± 2.8	76 ± 2.9**	76 ± 2.4*	76 ± 2.7*	75 ± 2.7*	85 ± 3.6
Hyoscine	0.5	oral	73 ± 2.5	71 ± 2.5*	72 ± 2.4	73 ± 2.5	75 ± 2.6	85 ± 3.9**
Hyoscine	1.0	oral	70 ± 2.3	68 ± 2.3*	68 ± 2.7	65 ± 2.4*	68 ± 2.3	77 ± 3.3*
Glycopyrronium	0.1	i.m.	77 ± 3.5	75 ± 2.9*	75 ± 3.3	73 ± 3.7*	78 ± 3.8	88 ± 4.0**
Glycopyrronium	0.2	i.m.	70 ± 2.4	71 ± 2.2	72 ± 2.6	72 ± 2.4	74 ± 2.7	89 ± 3.0**
Glycopyrronium	0.4	i.m.	77 ± 2.4	76 ± 2.4	81 ± 3.3	87 ± 3.0**	92 ± 3.8**	99 ± 4.7**
Glycopyrronium	2.0	oral	77 ± 2.0	75 ± 1.8	75 ± 2.0	77 ± 2.3	77 ± 2.8	85 ± 3.5*
Glycopyrronium	4.0	oral	75 ± 2.4	74 ± 2.3	74 ± 1.9	76 ± 2.6	77 ± 2.6	85 ± 3.0**
Glycopyrronium	8.0	oral	73 ± 2.3	73 ± 2.7*	72 ± 2.5*	74 ± 3.0	78 ± 4.3	91 ± 4.0**
Placebo			72 ± 2.2	71 ± 2.2	71 ± 2.0	72 ± 2.1	73 ± 2.4	86 ± 2.7**

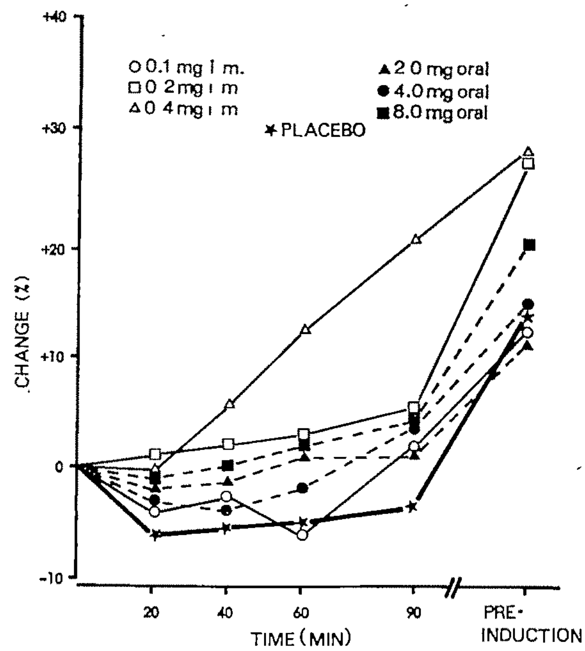

FIG. 3. Percentage changes in heart rate following administration of three doses of glycopyrronium by oral and i.m. routes.

Temperature

There was a minimal, although statistically significant, increase ($P < 0.05$) in temperature in all the groups, the maximum increase being 0.3 °C.

Pupil size

Hyoscine i.m. had the most marked effect on pupil size, producing significant ($P < 0.05$) dilatation with all three doses. The other drugs produced significant dilatation only with the highest doses, glycopyrronium producing the least effects.

Subjective dryness

The frequency of the various grades of subjective dryness before premedication was similar in all the groups (table III). Although the patients who received their premedications i.m. started to feel dry at 40 min, this was significant ($P < 0.05$) only in the case of hyoscine 0.5 mg (moderately dry and dry grades grouped together for statistical analysis).

All doses of atropine i.m. produced significant ($P < 0.001$) dryness at 60 min, followed by only a marginal increase at 90 min. All doses of oral atropine produced significant dryness at 90 min although 2.0 mg produced significant dryness at 60 min also. Two milligram orally had an effect similar to that

TABLE III. *Percentage frequency of various degrees of dryness as assessed by the patients at the times shown and by anaesthetist*

			Before premed.			At 60 min			At 90 min			Anaesthetist's assessment		
Drug	Dose (mg)	Route	Dry	Mod. dry	Wet	Dry	Mod. dry	Wet	Dry	Mod. dry	Wet	Dry	Mod. dry	Wet
Atropine	0.5	i.m.	0	5	95	10	60	30	15	70	15	30	60	10
Atropine	1.0	i.m.	0	15	85	10	75	15	15	80	5	50	45	5
Atropine	2.0	i.m.	0	15	85	25	75	0	60	40	0	30	50	20
Atropine	0.5	oral	0	10	90	10	20	70	10	50	40	15	55	30
Atropine	1.0	oral	0	20	80	20	30	50	20	60	20	45	40	15
Atropine	2.0	oral	0	25	75	25	45	30	25	60	15	55	40	5
Hyoscine	0.25	i.m.	0	25	75	15	60	25	25	60	15	40	60	0
Hyoscine	0.5	i.m.	0	20	80	30	60	10	50	50	0	50	50	0
Hyoscine	1.0	i.m.	0	35	65	15	80	5	35	60	5	60	30	10
Hyoscine	0.25	oral	0	20	80	0	35	65	0	50	50	5	50	45
Hyoscine	0.5	oral	0	20	80	10	40	50	10	60	30	25	55	20
Hyoscine	1.0	oral	0	20	80	0	60	40	5	65	30	65	30	5
Glycopyrronium	0.1	i.m.	0	15	85	0	25	75	5	40	55	25	50	25
Glycopyrronium	0.2	i.m.	0	15	85	0	65	35	5	85	10	50	45	5
Glycopyrronium	0.4	i.m.	0	25	75	10	70	20	20	80	0	55	40	5
Glycopyrronium	2.0	oral	0	35	65	10	45	45	15	60	25	25	60	15
Glycopyrronium	4.0	oral	0	15	85	0	35	65	0	50	50	15	55	30
Glycopyrronium	8.0	oral	0	20	80	0	40	60	5	65	30	30	60	10
Placebo			0	30	70	5	30	65	5	40	60	5	40	55

of 1.0 mg i.m. The majority of the patients having any dose of hyoscine i.m. were dry at 60 min with little further change at 90 min, both being significant ($P < 0.05$). When administered orally only 1.0 mg produced significant dryness at 60 min whereas 0.5 and 1.0 mg produced significant dryness at 90 min, 0.25 mg i.m. and 1.0 mg orally appearing to be equipotent. The dryness following oral glycopyrronium was significant only at 90 min. Following i.m. administration 0.2 and 0.4 mg produced significant ($P < 0.05$) dryness at 60 min, and at 90 min nearly all patients were dry with these two doses. The frequency of dryness following placebo administration was insignificant at both 60 and 90 min.

The observer assessment of secretions by the anaesthetist closely paralleled the subjective feelings of the patients (table III). In spite of some patients being classified as wet, the number in whom suction was required was small in all the series.

Other effects

A few patients complained of sleepiness after atropine and glycopyrronium, but this was a frequent occurrence with hyoscine; 1.0 mg i.m. gave rise to a 70% frequency of drowsiness. Half the patients receiving hyoscine 1.0 mg i.m. experienced also intense restlessness or disorientation, or both. One patient receiving atropine 2.0 mg i.m. complained of palpitations. No patient complained of visual difficulty before operation, but about one-third of patients receiving the two larger doses of hyoscine i.m. encountered visual difficulty in the period after operation.

The patients were anaesthetized approximately 125 min following premedication and in most the induction and maintenance of anaesthesia was without difficulty. The duration of anaesthesia was 7–10 min. Two patients exhibited bradycardia and some cardiac irregularity, but treatment was not required.

DISCUSSION

The popularity of the belladona compounds as part of routine preanaesthetic medication stems mainly from their antisialogogue and vagolytic actions. Excessive secretion has ceased to be a major problem. Secretions are troublesome only if these are excessive and interfere with the smooth conduct of anaesthesia. This was not the case in the present study; very few patients required oropharyngeal suction and the conduct of anaesthesia was similar in all the groups. In fact Eger (1962), Clarke, Dundee and Moore (1964) and Gravenstein and Anton (1969) have suggested that drugs such as atropine need not be administered for operations of short duration. In the present study tracheal intubation was performed on a small minority of patients and it may not be correct to extend the conclusions to intubated patients. However, Kessell (1974) and Leighton and Sanders (1976) encountered no problems from the omission of anticholinergic premedicants even in intubated patients. Falick and Smiler (1975), on the other hand, found conditions during anaesthesia to be superior following such premedication. Atropine can make the secretions viscid and has been shown to diminish the efficiency of the cilia (Annis, Landa and Lichtiger, 1976).

The prevention of vagal overactivity is considered the second important function of atropine-like drugs, but atropine itself may cause unnecessary tachycardia and arrhythmia (Jones, Deutsch and Turndorf, 1961; Eger, 1962; Farman, 1967). The administration of a single dose of suxamethonium is not associated normally with slowing of heart rate (Lupprian and Churchill-Davidson, 1960) and the usual response to laryngoscopy and tracheal intubation is tachycardia and an increase in arterial pressure (King et al., 1951; Wycoff, 1960; Forbes and Dally, 1970). Atropine may have a sympathetic stimulating action (Holt, 1962; Thurlow, 1972) and this will predispose to arrhythmia. The situation may be different in children in whom suxamethonium may produce a decrease in heart rate (Leigh et al., 1957).

Detailed cardiovascular monitoring was not carried out in the present study. However, it is worth recalling the study by Dobkin (1959) in which patients undergoing e.c.t. were suspected of having a period of cardiac asystole when no anticholinergic premedication was administered. In our study patients undergoing e.c.t. were distributed amongst the various groups and, although no e.c.g. monitoring was carried out, the course of anaesthesia and shock treatment was generally satisfactory in all the groups.

Only the greatest i.m. dose of glycopyrronium produced significant tachycardia. This was contrary to our observations in volunteers (Mirakhur et al., 1978) but was noticed by Oduro (1975) in patients following the administration of 0.2 mg. Atropine i.m. produced greater preoperative tachycardia than other drugs, but this may reflect a lack of sedation. The present study could not demonstrate any difference between glycopyrronium and the two standard anticholinergic drugs. However, a detailed study of cardiac rate and rhythm during the induction of anaesthesia showed glycopyrronium to be associated with a lower frequency of arrhythmia (Mirakhur, 1977). Although there was obviously a delay in attaining its peak effect, it was apparent that atropine was absorbed well from the gastrointestinal tract. A detailed study in volunteers showed 1.0 mg i.m. and 2.0 mg orally to have an equivalent antisialogogue and cardiac vagolytic effect (Mirakhur, 1978). Although at 60 min 1.0 mg i.m. was the more effective, allowing adequate time for the development of the peak action of orally administered atropine improved the frequency and quality of dryness at 90 min and during anaesthesia. Absorption of oral atropine has been well demonstrated by Joseph and Vale (1960), Möller and Rosen (1968) and Murrin (1973). The gastrointestinal absorption of hyoscine appears to be poor as compared with atropine and this has been shown in volunteers (Mirakhur, 1978). However, according to the anaesthetist's assessment in this study, 0.5 mg i.m. and 1.0 mg orally appeared to produce a similar degree of dryness.

The optimum dose of glycopyrronium i.m. appeared to be 0.2 mg and little was gained by increasing the dose. Since it is a quaternary ammonium compound absorption from the gastrointestinal tract would be expected to be poor (Innes and Nickerson, 1975). Although the present study did not bear this out, an earlier study in volunteers (Mirakhur et al., 1978) demonstrated a delayed and inconsistent action and the need for large oral doses. The advantageous properties of glycopyrronium are its lack of central action, visual disturbances and serious cardiovascular effects.

It appears from this study that the reduction of secretions is the only positive effect of anticholinergic premedication in patients undergoing minor surgery. However, this does not contribute anything useful to the conduct of smooth anaesthesia in such cases. The routine use of such preanaesthetic medication does not seem to be necessary.

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ETUDES SUR LES MEDICAMENTS ADMINISTRES AVANT L'ANESTHESIE. XVII: PREMEDICATIONS ANTICHOLINERGIQUES

RESUME

On a procédé à une estimation des effets découlant de prémédications basées sur les médicaments anticholinergiques suivants: atropine, hyoscine et glycopyrronium, administrés soit par voie orale, soit par voie intramusculaire, sur des malades devant être soumis à des interventions chirurgicales mineures, puis on a comparé les résultats à ceux d'un placébo, en employant une technique à double inconnue basée sur deux médicaments factices. Bien que la bouche des malades auxquels on avait administré des doses adéquates de médicaments anticholinergiques était subjectivement et objectivement sèche lorsqu'on l'a comparée à celle des malades ayant reçu un placébo, la séquence d'ensemble des opérations d'anesthésie ne semble pas avoir été différente. Sur ces trois médicaments l'atropine semble avoir été la mieux assimilée, après administration par voie orale. On considère que des doses d'atropine de 2 mg et de 1 mg administrées respectivement par voie orale et par voie intramusculaire sont également efficaces. En ce qui concerne l'hyoscine, ces doses sont respectivement 1 mg et 0,25–0,50 mg. La dose appropriée de glycopyrronium a été de 0,2 mg (par voie intramusculaire). L'usage routinier de médicaments anticholinergiques dans les médications préanesthésiques pour les interventions chirurgicales mineures semble inutile.

UNTERSUCHUNGEN ÜBER VOR ANÄSTHESIE VERABREICHTE DROGEN. XVII: ANTICHOLINERGISCHE VORBEHANDLUNGSMITTEL

ZUSAMMENFASSUNG

Die Wirkunge der Vorbehandlung mit oral und intramuskulär verabreichten anticholinergischen Drogen wie Atropin, Hycosin und Glycopyrronium wurden bei Patienten untersucht, die kleineren Operationen unterzogen wurden, und wurden mit einem Plazebo mittels einer Doppel-Plazebo, Doppelblind-Methode verglichen. Obwohl der Mund jener Patienten, die entsprechende Dosen anticholinergischer Drogen erhielten, dazu neigte, trockener zu sein als der von Plazebo-Patienten, schien der allgemeine Verlauf der Narkose nicht unterschiedlich zu sein. Von den drei erwähnten Drogen schien oral verabreichtes Atropin am besten absorbiert zu werden. Gleichermassen wirksame Dosen von oral und intramuskular verabreichtem Atropin sind 2,0, bezw. 1,0 mg; fur Hycosin 1,0 bezw. 0,25–0,5 mg, und fur Glycopyrronium 0,2 mg intramuskulär. Die routinemässige Verwendung anticholinergischer Drogen zur Vornarkosebehandlung bei kleineren Operationen erscheint unnötig.

ESTUDIOS SOBRE DROGAS DADAS ANTES DE LA ANESTESIA. XVII: PREMEDICAMENTOS ANTICOLINERGICOS

SUMARIO

Se han evaluado los efectos de premedicación con las drogas anticolinérgicas atropina, hioscina y glicopirronio cuando son administradas oral e intramuscularmente en pacientes sometidos a cirugía menor, comparándose con un placebo, mediante la aplicación de una técnica de doble simulación y doble anonimato. Aunque la boca de aquellos pacientes que recibieron dosis adecuadas de drogas anticolinérgicas resultó más seca, según se observó subjetivamente en comparación con aquellos que habían recibido el placebo, el curso general de la anestesia no pareció diferente. De las tres drogas, la atropina pareció absorberse mejor tras la administración oral. Se consideró que las dosis de atropina oral e intramusculares de efectividad equivalente eran de 2,0 y 1,0 mg, respectivamente; de hioscina, 1,0 y 0,25–0,5 mg. La dosis apropiada de glicopirronio fue de 0,2 i.m. El empleo rutinario de drogas anticolinérgicas en la medicación preanestésica para cirugía menor parece ser innecesario.

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EFFECT OF ETOMIDATE ON INTRACRANIAL PRESSURE AND CEREBRAL PERFUSION PRESSURE

E. MOSS, D. POWELL, R. M. GIBSON AND D. G. McDOWALL

SUMMARY

Ten patients with intracranial lesions, anaesthetized with thiopentone and nitrous oxide (70%) in oxygen (30%) received etomidate 0.2 mg kg^{-1} i.v. Ventilation was controlled in each patient. Intracranial pressure (i.c.p.) and mean arterial pressure (m.a.p.) were recorded. I.c.p. decreased significantly in all patients ($0.01 > P > 0.001$). Although Pa_{CO_2} decreased during the period of measurement, the extent and time-course of this change suggested that it was not mainly responsible for changes in i.c.p. M.a.p. decreased in most patients, but the decrease was statistically significant only at 3 and 4 min after the administration of etomidate ($0.05 > P > 0.02$). The changes in cerebral perfusion pressure (c.p.p.) and heart rate were not clinically or statistically significant. We conclude that etomidate can be used for the induction of anaesthesia in patients with intracranial space-occupying lesions without increasing i.c.p. or seriously reducing c.p.p.

All the agents used commonly i.v. to induce anaesthesia have been shown to decrease intracranial pressure (i.c.p.) (Horsley, 1937; Hunter, 1972; Turner et al., 1973) and cerebral blood flow (c.b.f.) (Pierce et al., 1962; Herrschaft et al., 1975; Sari et al., 1976), with the sole exception of ketamine, which increases both i.c.p. (Evans et al., 1971; Gardner, Olson and Lichtiger, 1971; Takeshita, Okuda and Sari, 1972) and c.b.f. (Dawson, Michenfelder and Theye, 1971; Takeshita, Okuda and Sari, 1972). Etomidate, an i.v. agent, has been introduced recently for induction of anaesthesia and has the advantages of cardiovascular stability (Doenicke, 1974; Morgan, Lumley and Whitwam, 1975; Holdcroft et al., 1976; Rifat, Gamulin and Gemperle, 1976; Famewo and Odugbesan, 1977; Ghoneim and Yamada, 1977; Lees and Hendry, 1977; Patschke et al., 1977), freedom from marked respiratory depression (Doenicke, 1974; Morgan, Lumley and Whitwam, 1975, 1977; Famewo and Odugbesan, 1977, 1978; Ghoneim and Yamada, 1977), and rapid inactivation (Kay, 1976; Lees and Hendry, 1977). It has been shown by Herrschaft and his co-workers (1975) that etomidate decreases c.b.f. in normal man, and thus it would be expected to reduce i.c.p. also. This study was undertaken to determine the effect of etomidate on i.c.p. in patients with intracranial pathology who were about to undergo craniotomy, and thus to determine its suitability for use in patients with intracranial space-occupying lesions.

METHODS

Ten patients with intracranial lesions requiring craniotomy were investigated. All gave their informed consent for the study. If considered necessary, the patients were premedicated with diazepam 10 mg i.m. Anaesthesia was induced with thiopentone, which was given until the eyelash reflex was obtunded, and was maintained with nitrous oxide 70% in oxygen. Ventilation was controlled using a Manley Pulmovent ventilator and tubocurarine 45 mg was administered to produce neuromuscular blockade. The volume of ventilation was adjusted to produce normocapnia and this was maintained constant throughout the period of the study. Allen's test was performed on all the patients and, if there was adequate ulnar collateral circulation, a radial artery cannula was inserted. After infiltration of the scalp with local analgesic a burr hole was made, through which a catheter was inserted into a lateral ventricle. The radial artery and ventricular cannulae were connected to suitably calibrated transducers, the signals from which were amplified and recorded on chart recorders. The zero reference for the arterial transducer was the mid-axillary line (with the patient supine, tilted 10° head-up), and for the ventricular transducer was the external auditory meatus. The arterial pressure and intracranial pressure traces were observed for 5 min before the injection of etomidate 0.2 mg kg^{-1} body

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weight given i.v. over a period of 10 s. The arterial pressure and i.c.p. were recorded for 10 min after the administration of the etomidate and before surgery was continued. Cerebral perfusion pressure (c.p.p.) was calculated by subtracting mean i.c.p. from the mean arterial pressure (m.a.p.). From the recordings, the following measurements were made: (i) m.a.p., mean i.c.p. and c.p.p. in the 5 min before the injection of etomidate (control values for m.a.p., mean i.c.p. and c.p.p.); (ii) m.a.p., mean i.c.p. and c.p.p. at 1-min intervals for 10 min after the administration of the etomidate. (Only the results obtained at 2-min intervals are tabulated.)

Samples were taken for measurement of arterial blood-gas tensions just before the administration of the etomidate (initial Pa_{CO_2}) and at 10 min after the administration of etomidate (final Pa_{CO_2}). During the period of measurement the end-tidal carbon dioxide concentration was monitored continuously with an infra-red gas analyser.

RESULTS

The ages and diagnoses of all the patients and their mean i.c.p. during the control period, and at 2-min intervals after the administration of etomidate are in table I. It was found that i.c.p. decreased initially in all the patients and then started to increase, but in only two patients, it returned to control values within the 10 min (fig. 1). This decrease from control was statistically significant ($0.01 > P > 0.001$) at the 1st min after injection, and remained significant at the 1% level or greater for the 10 min of measurement.

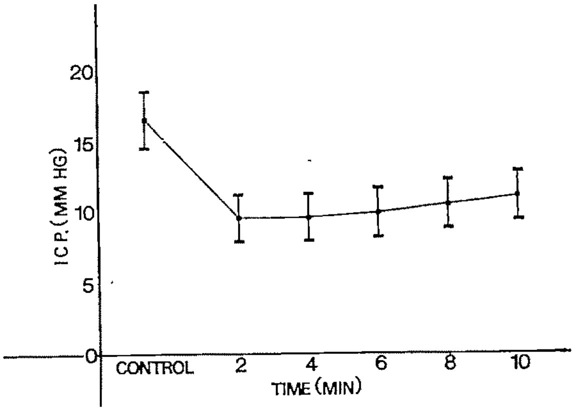

FIG. 1. The average i.c.p. (±SEM) (mm Hg) for the 10 patients before (control) and after the administration of etomidate 0.2 mg kg^{-1}.

There was a small decrease in m.a.p. in eight patients which was significant statistically at 3 and 4 min after the administration of etomidate ($0.05 > P > 0.02$) (table II). The heart rate decreased slightly in eight patients but did not differ significantly from the control value at any time.

On average c.p.p. decreased slightly, but this decrease never reached statistical significance (table III, fig. 2). In only one patient did the c.p.p. decrease to less than 60 mm Hg (patient B, minimum c.p.p. = 54 mm Hg).

TABLE I. *The mean intracranial pressure (mm Hg), diagnoses and ages (yr) of the 10 patients. Control indicates the mean pressure in the 5 min before administration of etomidate. The probability values represent the significance of the changes in i.c.p. from the control value*

Patient and age (yr)	Diagnosis	Control i.c.p.	2 min	4 min	6 min	8 min	10 min
A (51)	Aneurysm	14	9	9	6	8	8
B (46)	Pituitary tumour	28	22	22	23	23	23
C (35)	Glioblastoma	16	10	11	12	14	16
D (22)	Glioblastoma	16	11	11	11	12	13
E (66)	Pituitary tumour	9	4	4	4	5	6
F (71)	Pituitary tumour	9	6	5	6	6	6
G (70)	Pituitary tumour	13	6	6	6	6	6
H (33)	Pituitary tumour	26	11	11	12	11	13
I (61)	Glioblastoma	21	8	7	8	8	9
J (51)	Meningioma	12	9	10	10	11	11
$\bar{x}$		16.4	9.6	9.6	9.8	10.4	11.1
SD		6.62	4.93	5.08	5.43	5.32	5.43
SEM		2.09	1.56	1.61	1.72	1.68	1.72
P			0.001	<0.001	<0.001	$0.01 > P > 0.001$	$0.01 > P > 0.001$

TABLE II. *The mean arterial pressure (mm Hg) of the 10 patients. "Control" indicates the mean pressure in the 5 min before the administration of etomidate. The probability value represents the significance of the change in m.a.p. from the control value*

Patient	Control	2 min	4 min	6 min	8 min	10 min
A	183	185	175	180	180	180
B	102	87	78	77	83	90
C	123	123	122	128	133	135
D	108	108	108	108	108	103
E	87	83	78	83	85	85
F	115	107	107	122	125	120
G	102	93	95	95	90	90
H	133	128	130	140	133	137
I	107	107	105	105	100	100
J	143	112	105	98	103	103
$\bar{x}$	120.3	113.3	110.3	113.6	114.0	114.3
SD	27.39	29.03	28.10	30.47	29.68	29.42
SEM	8.66	9.18	8.89	9.64	9.39	9.30
P			$0.05>P>0.02$			

TABLE III. *The cerebral perfusion pressure (mm Hg) of the 10 patients. "Control" indicates the mean cerebral perfusion pressure in the 5 min before the administration of etomidate*

Patient	Control	2 min	4 min	6 min	8 min	10 min
A	169	176	166	174	172	172
B	74	65	56	54	60	67
C	107	113	111	116	119	119
D	92	97	97	97	96	90
E	78	79	74	79	80	79
F	106	101	102	116	119	114
G	89	87	89	89	84	84
H	107	117	119	128	122	124
I	86	99	98	97	92	91
J	131	103	95	88	92	92
$\bar{x}$	103.9	103.7	100.7	103.8	103.6	103.2
SD	28.37	29.72	29.07	32.43	31.02	30.27
SEM	8.97	9.40	9.19	10.26	9.81	9.57

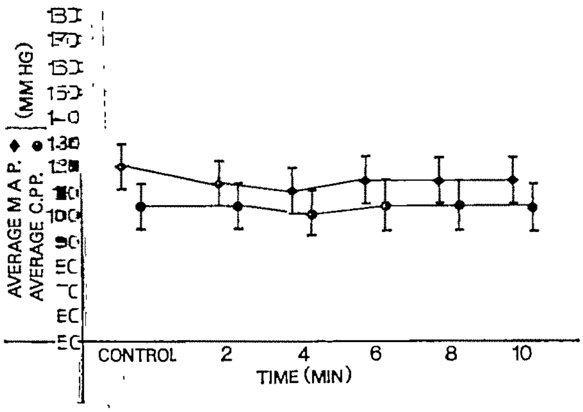

FIG. 2. The average m.a.p., average c.p.p. (±SEM) (mm Hg) for the 10 patients before (control) and after the administration of etomidate 0.2 mg kg^{-1}.

TABLE IV. *Pa_{CO_2} values (kPa) of the 10 patients immediately before the administration of etomidate (initial Pa_{CO_2}) and at 10 min after administration of etomidate (final Pa_{CO_2}). The probability value refers to the significance of the change in Pa_{CO_2} during the period of measurement*

Patient	Initial Pa_{CO_2}	Final Pa_{CO_2}
A	4.67	4.13
B	4.80	4.80
C	4.40	4.40
D	4.13	4.0
E	4.53	4.27
F	4.93	4.67
G	4.53	4.27
H	4.80	4.67
I	5.60	5.33
J	3.07	2.67
$\bar{x}$	4.55	4.32
SD	0.65	0.70
SEM	0.21	0.22
P	$0.01>P>0.001$	

It can be seen (table IV) that in five patients Pa_{CO_2} was in the lower part of the normal range, and in four patients just below the lower limit of normal. One patient was markedly hypocapnic. In most patients there was a slight decrease in Pa_{CO_2} over the 10-min period of measurement, so that mean Pa_{CO_2} decreased by 0.23 kPa (statistically significant: $0.01>P>0.001$). The decrease in the end-tidal carbon dioxide concentration occurred usually at between 2 and 7 min after the administration of etomidate.

Figure 3 shows the scatter diagram and regression line for the decrease in i.c.p. after the administration of etomidate plotted against the initial i.c.p. value. The correlation ($r = 0.624$) between decrease in i.c.p. and initial i.c.p. was not significant statistically.

DISCUSSION

It is known that thiopentone, methohexitone and Althesin reduce i.c.p. (Horsley, 1937; Hunter, 1972; Turner et al., 1973) and c.b.f. (Pierce et al., 1962; Herrschaft et al., 1975; Sari et al., 1976), but that ketamine increases i.c.p. (Evans et al., 1971; Gardner,

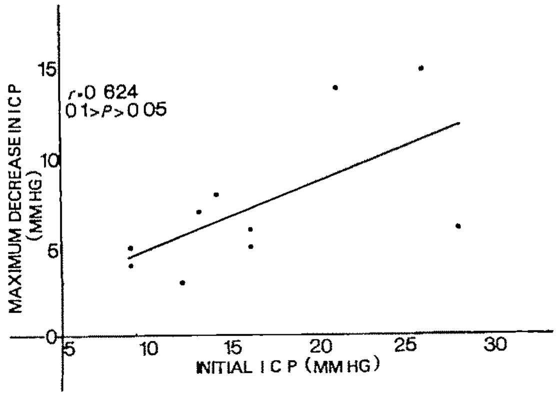

FIG. 3. Comparison of the maximum decrease in i.c.p. produced by etomidate with the initial i.c.p. value.

Olson and Lichtiger, 1971; Wyte et al., 1972) and c.b.f. (Dawson, Michenfelder and Theye, 1971; Takeshita, Okuda and Sari, 1972). In the presence of intracranial space-occupying lesions, it is preferable to use agents which either do not affect i.c.p. or which decrease it. Thus, it is important to determine the effect on i.c.p. of any new anaesthetic agent, such as etomidate, to ascertain its suitability for use in patients with increased i.c.p.

In this study there was a decrease in i.c.p. in all 10 patients following the administration of etomidate i.v. This reduction can be explained almost certainly by the rapid decrease in c.b.f., and thus cerebral blood volume, which is known to occur after the administration of etomidate (Herrschaft et al., 1975). Herrschaft's studies were in normal patients anaesthetized with propanidid, suxamethonium, nitrous oxide, oxygen and halothane 0.1–0.4 vol%. The use of halothane may explain the more short-lived reduction in c.b.f. that they observed (less than 5 min) as compared with the duration of the decrease in i.c.p. that we observed (more than 10 min). The duration of the decrease in i.c.p. seen in our study is more in keeping with the duration of action of etomidate reported in the literature both by Doenicke (1974), who reported that the time to complete recovery after the administration of etomidate 0.3 mg kg^{-1} was approximately 12 min, and by Lewi and Heykants (1978) who found that the plasma concentration decreased by approximately 90% in 16 min after a dose of 0.21 mg kg^{-1}. The numbers in this present series were inadequate to show whether there was a greater decrease in i.c.p. if the i.c.p. was high initially.

The small decrease in Pa_{CO_2} (average 0.23 kPa), noted in most of the patients during the period of measurement, occurred during constant ventilation which had been established for at least 30 min before the administration of etomidate. It may have been a result of a reduction in metabolic rate, and thus a reduction in carbon dioxide production. With one exception this decrease in Pa_{CO_2} occurred between 2 and 7 min after the administration of etomidate, whereas the maximum change in i.c.p. occurred within 90 s, and by 7 min i.c.p. was beginning to increase again. Thus, the influence on i.c.p. of this small change in Pa_{CO_2} was probably minimal.

Although the m.a.p. decreased in all but two patients, the lowest m.a.p. recorded was 77 mm Hg which was above the value at which the autoregulation of c.b.f. ceases and c.b.f. becomes pressure-dependent. The c.p.p. increased in 50% of the patients and decreased in 50%, remaining adequate in all. The heart rate decreased slightly in most of the patients, but the change was not significant statistically. These findings confirm the cardiovascular stability found with etomidate (Doenicke, 1974; Morgan, Lumley and Whitwam, 1975; Holdcroft et al., 1976; Rifat, Gamulin and Gemperle, 1976; Famewo and Odugbesan, 1977; Ghoneim and Yamada, 1977; Lees and Hendry, 1977; Patschke et al., 1977).

There are other possible advantages of etomidate which were not assessed in this study. Plasma histamine concentration does not increase after its administration (Doenicke et al., 1973) (whereas it does after Althesin and propanidid), and as yet there is no reported case of allergic reaction to the drug. In the dose required for anaesthesia, respiratory depression is not a problem (Doenicke, 1974; Morgan, Lumley and Whitwam, 1975, 1977; Famewo and Odugbesan, 1977, 1978; Ghoneim and Yamada, 1977), although this is not so important in neuroanaesthesia as ventilation is usually controlled. Etomidate is metabolized quickly and, judged on clinical grounds in man, is not cumulative (Kay, 1976; Lees and Hendry, 1977). Thus, its use by continuous i.v. infusion may have a place, as an alternative to methohexitone (Hunter, 1972) or Althesin, in maintaining anaesthesia in patients with intracranial space-occupying lesions. The rapid metabolism of the drug and its ability to reduce i.c.p. suggest that it would be suitable for the rapid reduction of i.c.p. in patients with head injuries, or for prophylactic use before chest physiotherapy or other procedures known to increase i.c.p. in this group of patients.

On the basis of this study, we conclude that etomidate would be a useful addition to the drugs available to the neuroanaesthetist for the induction of anaesthesia, a conclusion which is supported by recent reports by Cunitz, Danhauser and Wickbold (1978) and Schulte am Esch, Pfeifer and Thiemig (1978). In addition, it could be used as an agent for the rapid reduction of i.c.p. and possibly for maintenance of anaesthesia by continuous infusion.

Note added in proof: Since this manuscript was prepared, Renou and colleagues (1978) have published work showing a reduction in c.b.f. following etomidate in patients with intracranial pathology.

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EFFET DE L'ETOMIDATE SUR LA PRESSION INTERCRANIENNE ET SUR LA PRESSION DE PERFUSION CEREBRALE

RESUME

Dix malades ayant des lésions intracrâniennes, anesthésiés au thiopentone et au protoxyde d'azote (70%) dans l'oxygène (30%) ont reçu de l'étomidate par voie intraveineuse à raison de 0,2 mg kg^{-1}. La ventilation a été contrôlée sur

chaque patient. La pression intracrânienne (ICP) et la pression artérielle moyenne (MAP) ont été enregistrées. L'ICP a diminué d'une manière significative chez tous les malades ($0,01 > P > 0,001$). Bien que la Pa_{CO_2} ait diminué pendant la période ou l'on a pris les mesures, l'importance et le temps de ce changement laissent penser que celle-ci n'a pas été essentiellement responsable des variations de l'ICP. La MAP a diminué chez la plupart des patients, mais cette diminution n'a eu d'importance statistique que 3 et 4 min après l'administration d'étomidate ($0,05 > P > 0,02$). Les variations de la pression de la perfusion cérébrale (CPP) et de la fréquence cardiaque n'ont eu aucune importance clinique ou statistique. Nous en concluons que l'étomidate peut être utilisé pour l'induction de l'anesthésie sur les malades ayant des lésions intracrâniennes envahissantes et qu'il ne fait pas augmenter l'ICP ou diminuer sérieusement la CPP.

DIE WIRKUNG VON ETOMIDAT AUF INTRAKRANIELLEN UND ZEREBRALEN PERFUSIONSDRUCK

ZUSAMMENFASSUNG

Zehn Patienten mit intrakraniellen Verletzungen erhielten intravenos $0,2\ \mathrm{mg\ kg^{-1}}$ Etomidat, während sie mit Thiopenton und Stickoxyd (70%) in Sauerstoff (30%) narkotisiert waren. Die Beatmung wurde bei allen Patienten kontrolliert. Der intrakranielle Druck (I.C.P.) und der mittlere arterielle Druck (M.A.P.) wurden aufgezeichnet. I.C.P. sank wesentlich bei allen Patienten ($0,01 > P > 0,001$). Obwohl Pa_{CO_2} wahrend der Messungsperiode sank, deuteten Ausmass und Zeitablauf dieser Veränderung darauf hin, dass sie nicht in erster Linie für die Anderungen von I.C.P. verantwortlich war. M.A.P. sank bei den meisten Patienten, doch war diese Verringerung nur bei 3 und 4 Minuten nach der Verabreichung von Etomidat ($0,05 > P > 0,02$) statistisch von Bedeutung. Die Veränderungen des zerebralen Perfusionsdruckes (C.P.P.) und die Herztätigkeit waren klinisch oder statistisch unbedeutend. Wir schliessen daraus, dass Etomidat fur die Einleitung von Narkose bei Patienten mit intrakraniellen grosseren Verletzungen verwendet werden kann, ohne I.C.P. zu erhöhen oder C.P.P. ernsthaft zu verringern.

EFECTO EJERCIDO POR ETOMIDATA SOBRE LA PRESION INTRACRANEAL Y PRESION DE PERFUSION CEREBRAL

SUMARIO

Diez pacientes con lesiones intracraneales, anestesiados con tiopentona y oxido nitroso (70%) en oxígeno (30%), recibieron etomidata $0,2\ \mathrm{mg\ kg^{-1}}$ intravenosamente. La ventilación fue controlada en todos los pacientes. Se registró la presión intracraneal (I.C.P.) y presión arterial media (M.A.P.). La I.C.P. disminuyó significativamente en todos los pacientes ($0,01 > P > 0,001$). Aunque el Pa_{CO_2} disminuyó durante el período de medición, la magnitud y el transcurso de tiempo de este cambio sugirieron que no era principalmente responsable de los cambios en la I.C.P. La M.A.P. disminuyó en la mayoría de los pacientes, pero la disminución fue estadísticamente significativa solamente después de 3 y 4 min de administrarse etomidata ($0,05 > P > 0,02$). Los cambios en la presión de perfusión cerebral (C.P.P.) y en los latidos del corazón no fueron clínica ni estadísticamente significativos. Concluimos que la etomidata puede emplearse para la inducción de anestesia en pacientes con lesiones intracraneales que ocupan espacio, sin aumentar la I.C.P. ni reducir seriamente la C.P.P.

Br. J. Anaesth. (1979), **51**, 353

PRESYNAPTIC EFFECT OF I.V. ANAESTHETIC AGENTS AT THE NEUROMUSCULAR JUNCTION

T. A. TORDA AND E. C. MURPHY

SUMMARY

The effect of Althesin, diazepam, ketamine, propanidid and thiopentone on the release of acetylcholine was tested at the mouse neuromuscular junction. Althesin, diazepam and thiopentone increased the quantal content of the end-plate potential. Ketamine at low concentration (3.6 μmol litre^{-1}) had a similar effect, but at high concentration (116.7 μmol litre^{-1}) quantal content decreased sharply. Propanidid and cremophor EL did not affect quantal content. The increase in quantal content antagonized the effect of postsynaptic depression on the amplitude of the end-plate potential. The lack of enhancement of acetylcholine release appears to explain the *in vitro* interaction of propanidid with tubocurarine. The diversity of presynaptic actions of these drugs makes it unlikely that this is an important mechanism in producing anaesthesia.

It is now widely believed that general anaesthetics exert their effect through depression of synaptic function (Larrabee and Pasternak, 1952; Seeman, 1972). The synaptic depression appears to be the result of interference with the function of the ionic channels. The cause of this is the subject of a number of new hypotheses concerning anaesthetic action. Mullins (1954) proposed that, as anaesthetic molecules dissolve in the cell membrane, they fill "free volume". Subsequent work has modified this view, suggesting that volume expansion of the membrane occurs and results in compression of the entities within it (the ionic channels). Johnson and Miller (1970) proposed that anaesthetic molecules act by rendering the lipid in the cell membrane more fluid, thus altering the channel environment to the detriment of channel function. Hsia and Boggs (1975) suggested that anaesthetics acted directly on the protein moiety of the channel. Lee (1976) proposed that anaesthetics altered the channel environment by causing phase transition, a change in the state of the lipid from a liquid to a gel. Adams (1976), working specifically with barbiturates, proposed that anaesthetics block the active or open ionic channel. Finally, Trudell (1977) proposed that anaesthetics act by rendering nerve membranes fluid to a point at which critical lipid regions surrounding the channel no longer contain phase separations, thus impeding conformational changes in the channel protein. He also suggested that similar changes may affect release of transmitter. All these hypotheses treat the change in ionic conductance as a failure of channel function. All general anaesthetics tested so far (Gage and Hamill, 1976; Torda and Gage, 1977), including nitrous oxide at hyperbaric pressure (Torda and Hamill, unpublished data), reduce the duration of miniature end-plate currents, suggesting that premature closure of the channel, rather than a failure to open, underlies synaptic failure. As all the hypotheses are couched in general terms, none requires great modification to accommodate this view. All this work has concentrated on the postsynaptic or postjunctional effects of anaesthetics. It seemed desirable, therefore, to investigate the prejunctional effects of the i.v. anaesthetic drugs. As prejunctional factors influence transmission by altering transmitter release we examined the effect of i.v. anaesthetics on this index.

METHODS

The experiments were carried out on the excised mouse sternomastoid nerve–muscle preparation (Dulhunty, 1978). This was chosen in preference to the diaphragm as the larger muscle fibres permit long periods of intracellular recording without the use of electrodes of very high impedance. The nerve–muscle preparation was pinned out in a tissue bath of 3 ml

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TABLE I. *The effect of i.v. anaesthetic agents on the quantal content of the end-plate potential and its amplitude. The results are expressed as the ratio of the treated preparation to the control*

Drug	Concentration (μmol litre^{-1})	Concentration (mg litre^{-1})	No. of expts	Quantal cont. ratio ± SEM	P	Amplitude ratio ± SEM	P
Althesin	110	3.5*	10	2.64 ± 0.49	<0.01	1.50 ± 0.15	<0.01
	220	7*	10	1.21 ± 0.13	n.s.	1.05 ± 0.10	n.s.
Diazepam	140	40	5	2.88 ± 0.21	<0.01	1.40 ± 0.28	n.s.
Ketamine	3.6	1	4	1.60 ± 0.18	<0.05	1.08 ± 0.09	n.s.
	7.3	2	4	1.72 ± 0.31	n.s.	1.27 ± 0.21	n.s.
	58.4	16	6	1.28 ± 0.41	n.s.	0.63 ± 0.21	<0.01
	116.7	32	5	0.38 ± 0.15	<0.01	0.49 ± 0.09	<0.01
Propanidid	74	25	5	1.00 ± 0.18	n.s.	1.05 ± 0.06	n.s.
	148	50	5	1.01 ± 0.25	n.s.	0.77 ± 0.11	<0.05
Thiopentone	94.5	25	5	4.19 ± 1.20	<0.05	1.83 ± 0.60	n.s.
	189	50	5	2.69 ± 0.47	<0.05	1.67 ± 0.16	<0.05
Cremophor EL		4*	10	0.98 ± 0.18	n.s.	1.06 ± 0.09	n.s.

* ml litre^{-1}.

volume and perfused with Krebs solution* bubbled with 5% carbon dioxide in oxygen. The pH of the solution was between 7.35 and 7.45 unit and the experiments were carried out at 22 ± 1 °C.

To prevent movement of the preparation, the end plate potentials (EPP) were reduced below action potential threshold by the use of an increased concentration of magnesium in the solutions and this reduced the quanta of acetylcholine released per impulse (Del Castillo and Engbaek, 1954). As there was significant variation between preparations, the magnesium concentration was adjusted to produce EPP of about 2 mV. In order to maintain constant osmolality the concentration of sodium chloride was adjusted.

The nerve was stimulated by means of a suction electrode with supramaximal square wave stimuli of 0.1 ms duration at 0.5 Hz. The membrane potential and EPP were recorded with a conventional glass micro-electrode of 10–15 × 10^6 Ω impedance. All cells used in the experiments had membrane potentials in the range 60–80 mV. If the membrane potential decreased by more than 5 mV during an experiment, the data were discarded. In some experiments EPP were recorded on the screen of a storage oscilloscope. The amplitudes were measured and the mean and standard deviation were calculated. For other experiments, a computer performed these operations automatically. The quantal content (*m*), a measure of the amount of acetylcholine released by the EPP, was calculated from the variance ratio of the end-plate potentials (Del Castillo and Katz, 1954). As *m* was small, no correction was applied for non-linear summation. In each experiment at least 100 EPP were recorded. The order in which the preparation was exposed to control solution or solution containing the anaesthetic was alternated to exclude the effect of time. Each end-plate acted as its own control and the results are expressed as the ratio of *m* or EPP amplitude of the preparation in treated solution to that in control solution. The drugs tested were Althesin, diazepam, ketamine hydrochloride, propanidid, sodium thiopentone and cremophor EL. Althesin was assumed to contain 105 mg dl^{-1} of alphaxalone, based on the assumption that alphadolone acetate 30 mg is equivalent to 15 mg of alphaxalone.

RESULTS

Althesin in the smaller of the two concentrations tested, diazepam, ketamine at the smallest concentration and thiopentone increased *m* ($P < 0.05$ or < 0.01). Althesin in the greater and ketamine in intermediate concentrations did not alter *m* significantly ($P > 0.05$). Ketamine in the greatest concentration reduced *m*, while propanidid and cremophor EL did not appear to have any effect on the release of acetylcholine (table I).

The amplitude of the EPP was increased significantly ($P < 0.05$) by the small concentration of Althesin and the larger concentration of thiopentone.

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* Composition of the Krebs solution: sodium chloride 107–122 mmol litre^{-1}; potassium chloride 3.5 mmol litre^{-1}; sodium bicarbonate 24 mmol litre^{-1}; calcium chloride 2 mmol litre^{-1}; magnesium chloride 10–20 mmol litre^{-1}; glucose 11 mmol litre^{-1}.

It was decreased significantly by the two larger concentrations of ketamine and by the greater concentration of propanidid (table I).

The results suggest that Althesin and thiopentone may enhance release of acetylcholine in small concentrations and inhibit release in larger concentrations. The data demonstrate this in the case of ketamine.

DISCUSSION

Although the method used in these experiments is well accepted, recent work in the crayfish (Johnson and Wernig, 1971) and in the frog (Wernig, 1975) suggests that the probability of quantal release is a binomial, not a Poisson, function. If this is so, our calculations will tend to overestimate both increase and decrease in *m* by as much as 10%.

It has been shown previously that, in common with potent inhalation drugs (Gage and Hamill, 1976), all the drugs tested in this study reduce postsynaptic sensitivity (Torda and Gage, 1977). No uniformity could be demonstrated in their presynaptic action. The increase in quantal content (*m*) of the EPP caused by thiopentone confirms previous results in the frog with pentobarbitone and phenobarbitone (Thomson and Turkanis, 1973; Seyama and Narahashi, 1975; Proctor and Wakeley, 1976). The findings of Seyama and Narahashi support the suggestion gained from our data that it is only the smaller concentrations of some anaesthetic drugs which cause presynaptic facilitation. The other drugs studied had not been tested previously for such action.

The recorded amplitude of EPP is the result of the amount of acetylcholine released (*m*) and the postjunctional sensitivity. From a previous study (Torda and Gage, 1977) we know that all these drugs reduce the time constant of decay of the miniature end-plate current which indicates reduced postjunctional sensitivity. The amplitude ratio (table I) reflects the resultant of both pre- and postjunctional factors.

In interpreting our results the difficulty arises that the blood concentrations of these drugs associated with anaesthesia are not known. For ketamine the blood concentrations quoted by Johnston, Miller and Way (1974) probably reflect accurately the concentration at the neuromuscular junction during anaesthesia. Because this agent is relatively long acting the concentration in the cerebral circulation may not be very different. If that is so, the two smaller concentrations investigated are clinically relevant.

It is easier to apply our data to the interactions of anaesthetics and neuromuscular blocking drugs. In the case of propanidid the *in vitro* results of Ellis (1967), who demonstrated potentiation of tubocurarine by propanidid, are explained by postsynaptic depression without any increase in release of acetylcholine. Of course, *in vivo*, the short half-life of propanidid would prevent this interaction from becoming significant.

For ketamine the situation is more complex. Johnston, Miller and Way (1974) studied its interaction with tubocurarine, pancuronium and suxamethonium in patients anaesthetized with halothane, a drug with known depressant action at the neuromuscular junction (Gage and Hamill, 1976) by potentiating the competitive neuromuscular blockers (Gissen, Karis and Nastuk, 1966; Katz and Gissen, 1967). Under these complex circumstances, ketamine potentiated tubocurarine but not pancuronium. As the postjunctional actions of these drugs are similar while their prejunctional actions are not (Galindo, 1972), it can be postulated that tubocurarine but not pancuronium blocks the ketamine-induced increase in quantal content.

In the case of the other drugs (Althesin, diazepam and thiopentone), an increase in *m* is likely to mask any postsynaptic depressant effect at the neuromuscular junction, thus preventing any apparent interaction with neuromuscular blocking drugs.

Our results are of limited use in understanding the mode of action of anaesthetics. The neuromuscular junction is probably a good model of a central excitatory cholinergic synapse, but in the central nervous system acetylcholine may be both inhibitory and excitatory and there are at least seven other substances which may serve as neurotransmitters in the c.n.s. (Krnjevic, 1974). All anaesthetics tested cause postsynaptic depression at the neuromuscular junction, and the uniformity of this feature may be of significance. As yet we cannot place our findings in perspective regarding the presynaptic actions of the i.v. agents. If a "unitary theory" of anaesthesia is feasible, it will probably have to await a clearer understanding of the neuroanatomy and physiology of consciousness.

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EFFET PRESYNAPTIQUE DES AGENTS ANESTHESIANTS ADMINISTRES PAR VOIE INTRAVEINEUSE AUX COMMISSURES NEUROMUSCULAIRES

RESUME

On a procédé à des essais sur les effets de l'althésine, du diazépam, de la kétamine, du propanidid et du thiopentone sur le dégagement d'acétylcholine aux commissures neuromusculaires de la souris. L'althésine, le diazépam et le thiopentone ont fait augmenter la valeur quantique du potentiel de la plaque d'extrémité. La kétamine à faible concentration (3,6 μmol litre^{-1}) a eu un effet similaire, mais à forte concentration (116,7 μmol litre^{-1}) la valeur quantique a diminué brutalement. Le propanidid et le crémophor EL n'ont pas affecté la valeur quantique. L'augmentation de la valeur quantique a contrarié l'effet de dépression postsynaptique sur l'amplitude du potentiel de la plaque d'extrémité. Le manque d'augmentation du dégagement d'acétylcholine semble expliquer l'interaction *in vitro* du propanidid et de la tubocurarine. La diversité des actions présynaptiques de ces médicaments fait qu'il est invraisemblable que celles-ci constituent un mécanisme important de la production de l'anesthésie.

DIE PRÄSYNAPTISCHE WIRKUNG INTRAVENÖSER NARKOTIKA AN DER NEUROMUSKULÄREN VERBINDUNGSSTELLE

ZUSAMMENFASSUNG

Der Einfluss von Althesin, Diazepam, Ketamin, Propanidid und Thiopenton auf die Acetylcholinabgabe wurde an der neuromuskulären Verbindungsstelle in der Maus untersucht. Althesin, Diazepam und Thiopenton erhöhten den Quantalgehalt des Nervenendplattenpotentials. Ketamin in schwacher Konzentration (3,6 μmol liter^{-1}) hatte eine ahnliche Wirkung, aber bei starker Konzentration (116,7 μmol liter^{-1}) fiel der Quantalgehalt scharf ab. Propanidid und Cremophor-EL hatten keinen Einfluss auf den Quantalgehalt. Der Anstieg des Quantalgehalts wirkte dem Einfluss des postsynaptischen Absinkens auf die Amplitude des Endplattenpotentials entgegen. Die Erklärung fur die Wechselwirkung im Labor von Propanidid mit Tubocarin scheint in der mangelnden Erhöhung der Acetylcholinabgabe zu liegen. Die Vielfalt präsynaptischer Wirkungen dieser Drogen macht es unwahrscheinlich, dass es sich heir um einen wichtigen Mechanismus zur Bewirkung von Narkose handelt.

EFECTO PRESINAPTICO DE AGENTES ANESTESICOS I.V. EN LA JUNCION NEUROMUSCULAR

SUMARIO

Se probaron los efectos de Altesina, diazepam, ketamina, propanidida y tiopentona sobre la liberación de acetilcolina en la junción neuromuscular del ratón. La Altesina, el diazepam y la tiopentona aumentaron el contenido cuántico del potencial de la placa terminal. La ketamina en una concentración reducida (3,6 μmol litro^{-1}) ejerció un efecto semejante, pero en una concentración elevada (116,7 μmol litro^{-1}), el contenido cuántico disminuyó acentuadamente. La propanidida y el cremoforo EL no afectaron el contenido

cuántico. El aumento del contenido cuántico antagonizó al efecto ejercido por la depresión postsináptica sobre la amplitud del potencial de la placa terminal. La falta de acrecentamiento de la liberación de acetilcolina parece explicar la interacción *in vitro* de la propanidida con la tubocurarina. La diversidad de las acciones presinápticas de estas drogas hace poco probable que éste sea un importante mecanismo para producir anestesia.

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LABETALOL IN CONTROLLED HYPOTENSION

Administration of labetalol when adequate hypotension is difficult to achieve

D. H. P. COPE AND M. C. CRAWFORD

SUMMARY

A study of controlled hypotension was undertaken in 50 major surgical patients using labetalol, a drug with both alpha- and beta-adrenoceptor blocking activity. The patients were such that difficulty in achieving controlled hypotension could be anticipated: the young, the anxious and those for whom halothane was contraindicated. The administration of labetalol quickly induced hypotension which was controlled easily and was rapidly antagonized.

The introduction of halothane (Johnstone, 1956; Raventos, 1956) greatly facilitated the attainment of controlled hypotension during anaesthesia (Payne, 1963; Prys-Roberts et al., 1974). Its use with tubocurarine and controlled ventilation is now widely practised to reduce blood loss during major surgery, and in those operations where even a small amount of bleeding mitigates against a successful operative result, for example, middle ear surgery.

Nevertheless, there are a number of patients in whom this technique fails to produce adequate hypotension unless an undesirably high concentration of halothane is administered. In these circumstances, a ganglion blocking agent such as hexamethonium bromide (Walther, Slack and Chew, 1964) or trimetaphan (Hellewell and Potts, 1966) may be used in addition to gain the desired hypotension. However, these drugs are not entirely satisfactory; tachyphylaxis occurs and undesirable tachycardia is often induced. Propranolol (Hellewell and Potts, 1966; Hewitt, Lord and Thorton, 1967; Enderby, 1974) has been used to combat the increase in heart rate, but it is at the expense of an appreciable decrease in cardiac output (Prichard et al., 1975). Furthermore, hexamethonium has a prolonged duration of action so that, if the operation finishes earlier than expected, the arterial pressure may not be increased readily to a value at which obvious bleeding may be controlled unless vasopressor drugs are given.

Sodium nitroprusside (Bascombe and Lewis, 1968; Taylor, Styles and Lamming, 1970; Macrae, 1971; Griffiths et al., 1974) is an alternative hypotensive agent but it too may produce tachycardia (Moraca et al., 1962; Wildsmith et al., 1973). It is potentially toxic in that it produces a metabolic acidosis (Macrae and Owen, 1974) which may be lethal (Jack, 1974; Merrifield and Blundell, 1974). This acidosis occurs when large doses are given because of resistance or tachyphylaxis.

Patients in whom controlled hypotension is difficult to produce during surgery include younger patients with high sympathetic tone, anxious patients with tachycardia and those for whom halothane is contraindicated.

The introduction of labetalol (Boakes, Knight and Prichard, 1971; Richards et al., 1974), a combined alpha- and beta-adrenoceptor antagonist, in the medical treatment of hypertension was described by Prichard and others (1975) and Rosei and others (1975). It seemed that this drug might be pharmacologically useful for the production of controlled hypotension during anaesthesia in the types of patient described above. The alpha-adrenoceptors of the capacitance vessels may be blocked with resultant vasodilatation, and a reflex increase in heart rate and cardiac output may be prevented by the simultaneous blocking of the beta-receptors. Scott and others (1978) have investigated its use in anaesthesia for induced hypotension with halothane.

We describe the use of labetalol in 50 patients in the above categories.

PHARMACOLOGY AND METABOLISM

Labetalol hydrochloride (fig. 1) is an amide with competitive alpha- and beta-adrenoceptor antagonist properties (Richards, 1976).

Compared with propranolol, the β_1 antagonist effects are four to six times less potent on a weight basis and the β_2 (bronchial and vascular) blocking

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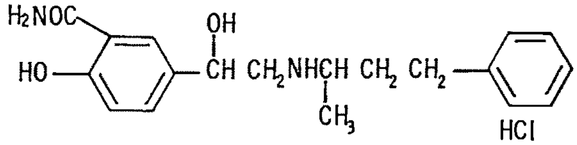

FIG. 1. Structure of labetalol.

effects are 11–17 times less potent. The alpha-antagonist effects are seven times less potent in comparison with phentolamine. Overall, the beta-blocking effects of labetalol are seven times as potent as the alpha-blocking effects.

Metabolism in man (Martin, Hopkins and Bland, 1976) is mainly associated with the first pass effect through the liver. Thus labetalol is metabolized to a greater extent following oral administration than when given i.v. The major glucuronide metabolite is as yet unidentified but a minor one already identified is O-phenylglucuronide. Both metabolites are found to have mild alpha- and beta-antagonist effects.

About 50% of labetalol is protein-bound. The major sites in the body where labetalol is found include the lungs, liver and kidneys. Labetalol is less lipophilic than propranolol or oxprenolol and virtually none has been found in brain tissue, whereas the other two drugs have been found in considerable quantities (Riess et al., 1970; Baker and Foulkes, 1973). This suggests that labetalol has probably only minimal central effects if any.

Sixty per cent of the metabolic products of labetalol are excreted in the urine and 40% in the faeces. Five per cent of that found in the urine is in the unchanged form. The half-life of elimination in man is 3.5–4.5 h (Martin, Hopkins and Bland, 1976).

PATIENTS AND TECHNIQUE

The average age of the patients was 40.9 yr (range 9–77 yr). If those to whom halothane was not administered are extracted, the average age was 38.8 yr. There were 29 males and 21 females. The operations in the study are shown in table I.

TABLE I.

Type of surgery	Operation	No. of patients	Total
Hip	Total hip replacement	12	
	Pin and plate	2	
	Pin and plate, osteotomy	1	
	Girdlestone	1	16
Spinal	Lumbo–sacral laminectomy	10	
	Lumbo-sacral fusion	4	
	Cervical fusion	2	16
Other orthopaedic	Putti Platt operation	2	
	Hindquarter amputation	1	
	Disarticulation hip	1	
	Replacement elbow + humerus	1	5
Nasal	Excision naso–pharyngeal angiofibroma	1	
	Rhinoplasty + septoplasty	1	
	Ethmoidectomy	1	
	Hypophysectomy	1	
	Excision biopsy cyst under eye	1	5
Ear	Myringoplasty	2	
	Mastoidectomy	2	4
Neck	Laryngectomy	1	
	Block dissection neck	1	
	Parotidectomy	1	3
General	Abdominoperineal resection	1	1

TABLE II.

Types of premedication	No. of patients
Pethidine, promethazine, hyoscine	39
Physeptone, promethazine, hyoscine	3
Papaveretum, hyoscine	2
Papaveretum, perphenazine, hyoscine	2
Papaveretum, promethazine, hyoscine	2
Pethidine, promethazine, atropine	1
Pethidine, perphenazine, hyoscine	1

All patients recieved i.m. premedication 1 h before surgery (table II). Anaesthesia was induced with thiopentone 2.5% solution, the average dose being 360 mg and in most instances (46) the trachea was intubated following suxamethonium i.v. In 29 patients the lungs were ventilated manually with nitrous oxide 3 litre and oxygen 1.5 litre. A Manley ventilator was used for 15 patients and six breathed spontaneously. Halothane was introduced in increasing concentration up to 2% and, as soon as there was evidence of muscle tone returning, tubocurarine 30 mg was given i.v. where necessary. The patients were transferred to the operating table and positioned for the operation. Arterial pressure measurements were made using the Von Recklinghausen oscillotonometer. We aimed to maintain arterial systolic pressure of 60–80 mm Hg during controlled hypotension. If it appeared that young or anxious patients would require more than 1% halothane to achieve this level then labetalol was administered.

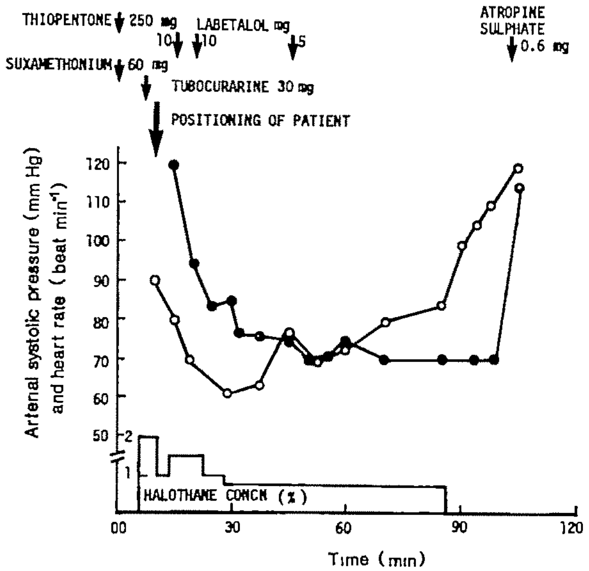

FIG. 2. Young patient with high sympathetic tone. Chart shows initial heart rate well controlled by labetalol and antagonized easily by atropine. (Thirteen-year-old female; nervous; lumbo-sacral spinal fusion for severe spondylolisthesis; premedication: pethidine 50 mg, promethazine 25 mg, hyoscine 0.2 mg.) ○——○ = arterial systolic pressure; ●——● = heart rate.

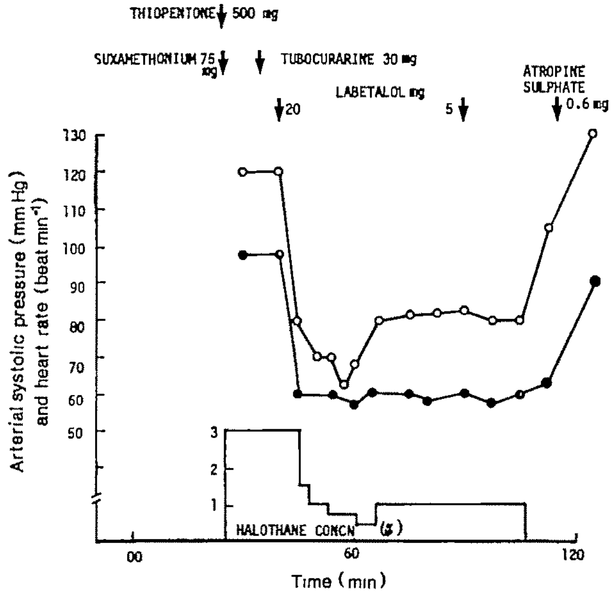

FIG. 3. Anxious patient with tachycardia. Chart shows initial tachycardia well controlled by labetalol and antagonized by atropine. (Thirty-year-old male; nervous; apprehensive; decompression L4–5, L5–S1, nerve roots and removal of prolapsed intervertebral discs; premedication: pethidine 100 mg, promethazine 25 mg, hyoscine 0.4 mg.) ○——○ = arterial systolic pressure; ●——● = heart rate.

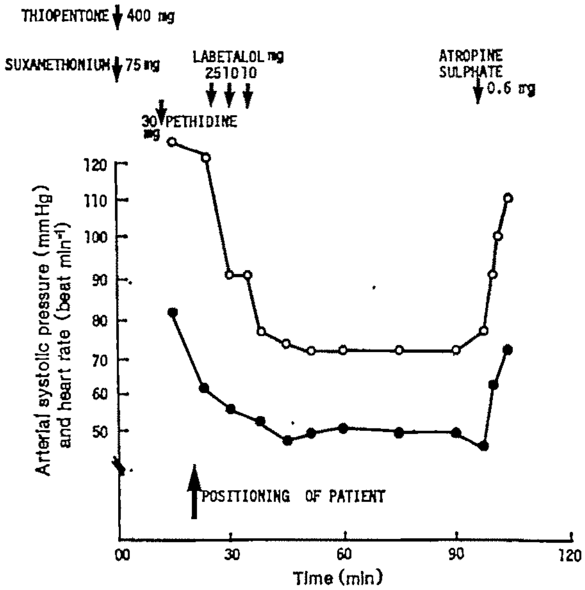

FIG. 4. Patient for whom halothane was contraindicated. Chart shows controlled hypotension in a patient to whom halothane was not administered. (Thirty-eight-year-old male; tympanoplasty; premedication: pethidine 75 mg, promethazine 25 mg, hyoscine 0.3 mg.) ○——○ = arterial systolic pressure; ●——● = heart rate.

Dose of labetalol

The initial dose of labetalol was assessed by the apparent resistance of the patient to the induction of hypotension and by the heart rate. The average amount for this dose of labetalol was 20 mg. If, after 5 min, the arterial systolic pressure had not decreased to the required value and the heart rate was still greater than 60 beat min^{-1}, further increments of 5–10 mg were given until the desired value was attained. It was important that the halothane concentration be reduced to approximately 1% when the initial dose was given or a profound decrease in arterial pressure might have occurred (Scott et al., 1978). In most instances, the regime produced an arterial systolic pressure in the range 60–80 mm Hg. This pressure could be controlled accurately by adjusting the concentration of halothane or by altering the pressure in the reservoir bag (Davison, 1962; Enderby, 1974).

Most of the surgeons preferred an arterial systolic pressure in excess of 100 mm Hg before commencing wound closure, and this was accomplished by decreasing the halothane concentration or by the administration of atropine 0.6 mg i.v. or both. At the end of the operation a further 0.6 mg of atropine with prostigmine 2.5 mg was given to antagonize any residual neuromuscular blockade.

A typical chart from each of the three categories of patient is presented in figures 2–4.

RESULTS

In those patients who were given halothane in concentrations of 2% or more without adequate hypotension being achieved, the administration of labetalol enabled the maintenance concentration of halothane to be reduced to about 1% or less.

Patients for whom halothane was contraindicated required a larger initial dose of labetalol, the average being 27.5 mg (range 25–30 mg) with subsequent increments of 10 mg. With this, hypotension was readily maintained (table III).

Five of the patients had a history of hypertensive ischaemic heart disease. Continuous e.c.g. recording in these patients failed to reveal any changes in character or rhythm apart from the drug-induced bradycardia.

The alpha effects lasted on average 32 min (range 7–97 min) and the beta effects 59 min (15–105 min). An intense stimulus during the operation occasionally caused an increase in arterial pressure without a change in heart rate.

The arterial pressure increased without a change in heart rate when halothane was discontinued. Following

TABLE III. *Amount of labetalol used during anaesthesia*

Dose	No. of patients	Dose of labetalol (mg)		Duration of effect (min)	
		Mean	Range	Mean	Range
1st	50	20.1	5–30	26.26	3–96
2nd	40	9.63	2.5–15	33.78	3–95
3rd	24	8.02	2.5–15	13.35	3–60
4th	11	8.86	2.5–15	21.03	3–80
Total	50	35.14	10–75	60.03	19–170
Total with halothane	46	33.1	10–75		
Total without halothane	4	48.75	40–65		
Initial dose without halothane	4	27.5	25–30		
Second dose without halothane	4	10	10		

TABLE IV. *Antagonism of labetalol-induced hypotension to an arterial systolic pressure greater than 100 mm Hg*

Method	Increase in arterial systolic pressure (mm Hg)		Increase in heart rate (beat min^{-1})		Time (min)	
	Mean	Range	Mean	Range	Mean	Range
Discontinuing halothane	15.7	1–45	6.98	0–35	7.88	3–30
Administration of atropine 0.6 mg	16.77	10–35	23.26	0–45	3.22	1–15

the i.v. administration of atropine sulphate 0.6 mg there was an almost immediate increase in the heart rate with a consequent increase in arterial pressure (table IV). All the patients were observed closely during the following 24 h and in no case was any residual block evident after operation.

DISCUSSION

The reduced blood loss during hypotensive anaesthesia may aid surgical exposure, minimize tissue trauma and improve healing after surgery. Such hypotension is often difficult to achieve with a combination of tubocurarine and halothane, especially in the young, the anxious and in those for whom halothane is contraindicated. Various drugs and techniques have been used in the past, but none is entirely satisfactory.

In this study, labetalol was used only when it became apparent that a high concentration of halothane or an additional agent was necessary to achieve the required arterial pressure. The result was satisfactory in that hypotension was attained quickly, maintained without difficulty and reversed readily in all cases. We believe that the initial dose of labetalol in adults should be 20 mg in those patients already receiving halothane, and that the concentration of the anaesthetic should be reduced simultaneously to 1%. Further increments of labetalol 5–10 mg may be given to attain the desired systolic arterial pressure provided that the heart rate is not less than 60 beat min^{-1}. In patients not receiving halothane, an initial dose of labetalol 30 mg may be given, and increments of 5–10 mg may be administered until the required systolic arterial pressure has been reached.

Five of the patients had a history of ischaemic heart disease. Labetalol would appear to be a useful agent for controlled hypotension in such cases, since Scott and others (1978) have shown that it reduces peripheral resistance, decreases heart rate and reduces cardiac output minimally in healthy patients. No abnormal e.c.g. changes occurred in any of our patients and there were no complications after operation.

The systolic arterial pressure may be restored rapidly to a "bleeding level" of 100 mm Hg before wound closure by administering atropine sulphate 0.6 mg. This reversal can be achieved as soon as 10 min after the last dose of labetalol with no recurrence of hypotension.

It must be remembered that as a result of the alpha- and beta-blocking effects of labetalol neither tachycardia nor vasoconstriction occur in response to haemorrhage. Unless the blood volume is maintained an undesirably low arterial pressure will ensue.

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USAGE DU LABETALOL POUR L'HYPOTENSION CONTROLEE

Administration de labétalol dans les cas où l'on éprouve des difficultés pour obtenir une hypotension adéquate

RESUME

Une étude de l'hypotension contrôlée a été entreprise sur 50 patients devant subir une intervention chirurgicale majeure, à l'aide de labétalol, médicament ayant la propriété de bloquer les adrénocepteurs alpha et béta. Les patients étaient dans un état tel que l'on prévoyait des difficultés pour obtenir une hypotension contrôlée: surtout les jeunes, les anxieux souffrant de tachycardie et ceux pour lesquels l'halothane était contre-indiquée. L'administration de labétalol a rapidement entraîné une hypotension que l'on a pu facilement contrôler et qui a été suivie d'une récupération rapide.

LABETALOL IN GESTEUERTER HYPOTONIE

Labetalolverabreichung in Fallen, bei denen entsprechende Hypotonie schwer erreichbar ist

ZUSAMMENFASSUNG

An 50 Grosschirurgiepatienten wurde unter Verwendung von Labetalol, einer Droge mit Blockierungswirkung auf sowohl den Alpha- wie auch den Beta-Adrenozeptor, die gesteuerte Hypotonie studiert. Die Kategorien der Patienten, die sich aus den Jungen, den Ängstlichen mit Tachykardie und denen, bei denen Halothan kontraindiziert war, zusammensetzten, liessen Schwierigkeiten im Erzielen einer gesteuerten Hypotonie erwarten. Die Verabreichung von Labetalol führte schnell zu einer leicht steuerbaren Hypotonie mit schneller Erholung.

LABETALOL EN HIPOTENSION CONTROLADA

Administración de labetalol en casos cuya hipotensión adecuada es difícil de lograr

SUMARIO

Se realizó un estudio de hipotensión controlada en 50 pacientes sometidos a cirugía mayor empleando labetalol, una droga con actividad de bloqueo adrenoceptor alfa y beta. Los pacientes eran de los que podía anticiparse dificultad en el logro de hipotensión controlada; los de corta edad, los ansiosos y aquellos para los cuales el halotano era contraindicado. La administración de labetalol indujo rápidamente la hipotensión, siendo ésta fácilmente controlada y lográndose una recuparación rápida.

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EXTRADURAL ANALGESIA FOR CAESAREAN SECTION: A COMPARISON WITH GENERAL ANAESTHESIA

J. W. Downing, P. C. Houlton and A. Barclay

SUMMARY

Thirty-two patients received lumbar extradural anaesthesia for elective Caesarean section. The results obtained from this series were compared with those from a similar (control) group of parturients who received general anaesthesia. The extradural group (mothers and infants) were metabolically acidaemic relative to control. However, maternal to fetal blood-gas differences were comparable in the two series. Infants sustained respiration more rapidly after regional blockade, otherwise the clinical condition of the infants was similar with extradural and general anaesthesia. No advantage of conduction over general anaesthesia was evident from this study, with respect to the biochemical status of the infant at birth.

The choice of anaesthetic technique for Caesarean section remains controversial. During general anaesthesia drug-induced depression of the newborn is proportional to the depth of anaesthesia (Belfrage et al., 1977) and, furthermore, the biochemical status of the fetus *in utero* may deteriorate with prolongation of the anaesthetic (Belfrage et al., 1977). In contrast, spinal and extradural analgesia may cause maternal hypotension and, consequently, there may be diminution of intervillous blood flow which may lead ultimately to fetal distress (Datta and Brown, 1977; Hollmén et al., 1978).

The popularity of extradural analgesia for elective Caesarean section continues to grow although the technique offers no advantage over general anaesthesia in terms of the biochemical condition of the mother and child (James et al., 1977; Lund et al., 1977; Palahniuk et al., 1977). However, extradural block does present a reasonable alternative to general anaesthesia for obstetrics, particularly when the operating time is expected to be prolonged (Belfrage et al., 1977).

Accordingly, we have studied the effects of lumbar extradural blockade for elective Caesarean section, comparing our results with those obtained from a previous but similar series of patients who received general anaesthesia (Buley et al., 1977).

METHODS

The programmes for both regional and general anaesthesia stipulated investigation of mothers categorized as "clinically acceptable ideal cases" (Crawford, Burton and Davies, 1973). Furthermore, standardized manœuvres which were designed to limit the adverse haemodynamic effects of aortocaval compression, starvation hypovolaemia and drug-induced vasodilatation, namely left lateral tilt and preloading with i.v. fluids, were used routinely during both extradural analgesia and general anaesthesia.

Thirty-two healthy parturients presenting for elective Caesarean section gave informed consent and were included in the study. The patients received 30 ml of mist. mag. trisilicate B.P.C. in the ward and were transferred to the operating theatre lying on the left side.

An i.v. infusion was established in the anaesthetic induction room and 500–1000 ml of balanced salt solution was given rapidly during the induction of extradural analgesia. Under sterile conditions and with the patient sitting upright, the extradural space (L2–3 or L3–4) was identified using a Tuohy needle and the loss of resistance to air technique. Thereafter 0.5% bupivacaine 14–20 ml with 1 in 200 000 adrenaline was injected slowly into the extradural compartment over 2–3 min. The patients were placed on the left side and the anaesthetic allowed to fix over 15–20 min, before moving to the operating theatre.

Elective Caesarean section was performed with the patient lying in the left lateral tilt position, breathing 40% oxygen via a Venturi mask (Mix-o-mask). Arterial pressure (Riva Rocci) and heart rate (by palpation or photoelectric finger transducer) were measured before the induction of anaesthesia and at 3–5-min intervals thereafter until the operation was complete. E.c.g. and heart rate (Data-scope 600

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Cardioscope) were monitored throughout the period of surgery. Any decrease in systolic arterial pressure was considered as an indication to increase the rate of i.v. infusion, elevate the patient's legs and, if necessary, administer a vasoconstrictor (metaraminol 0.5–1 mg) i.v. If the patient complained of pain or discomfort after the birth of the infant, analgesia was supplemented with 40% nitrous oxide in oxygen augmented by an i.v. injection of fentanyl 0.1 mg and droperidol 5 mg when necessary.

Under local anaesthesia a cannula was placed in the radial artery once the integrity of the collateral circulation to the hand had been established (Brodsky, 1975). A sample of maternal arterial blood was taken at the time of delivery. Fetal umbilical venous and arterial blood was obtained from a double-clamped section of cord immediately after birth of the infant. All blood samples were stored on ice and were analysed subsequently using International Laboratories IL 413 and Radiometer BMS Mk II blood-gas analysers. Hydrogen ion $[H^+]$ electrodes were calibrated using standard buffer solutions.

Calibration of the oxygen (Po_2) and carbon dioxide (Pco_2) electrodes was conducted using either certified gas mixtures (IL) or the Radiometer gas mixing device (carbon dioxide and air) and a zero oxygen solution. Base excess (BE) was derived from $[H^+]$ and Pco_2 using a Severinghaus slide rule (BGC 1) (Siggaard-Andersen, 1963). Corrections were made for the degree of desaturation of the haemoglobin present in the umbilical cord bloods using the nomogram prepared by Hellegers and Schruefer (1961).

The infants were awarded an Apgar score modified to exclude points for skin colour (Apgar minus colour) at 2 and 5 min following delivery (Crawford, Davies and Pearson, 1973). The time to sustained respiration (TSR) was measured accurately with a stop-watch to allow quantitative assessment of the clinical condition of the newborn at birth. Induction to delivery, surgical incision to delivery and uterine incision to delivery intervals were recorded also. The subsequent management of the newborn infants was according to our previous protocol (Buley et al., 1977).

Statistical analysis of our results (Student's t test for unpaired data and calculation of correlation coefficients—r values) was performed with the aid of a Hewlett-Packard 9815A programmed desk top calculator. Results obtained from the extradural group were compared with those from an earlier series of similar patients anaesthetized in the left lateral tilt position with thiopentone, 50 : 50 nitrous oxide in oxygen and enflurane 0.5–0.8%. This group received also neuromuscular blocking drugs and ventilation was controlled (Buley et al., 1977). The preanaesthetic management and the techniques of blood sampling and analysis used in the extradural group were identical to those used for the control series.

After delivery, the mothers who received general anaesthesia received a single i.v. injection of 1 ml of Syntometrine (ergometrine maleate 0.5 mg + oxytocin 5 i.u.) and oxytocin 20 i.u. was added to the i.v. infusion. Patients undergoing extradural analgesia received only oxytocin 20 i.u. by infusion, to avoid nausea and vomiting as a result of ergometrine present in Syntometrine.

RESULTS

Clinical data for both groups, detailing the average maternal age, weight and drug dosage, are shown in table I. The extradural group was, on average, younger than the control group ($P < 0.05$), but similar with respect to body mass. The mean dose of bupivacaine 0.5% with adrenaline 1 in 200 000 injected extradurally was 94.5 mg (SEM 1.0) or 18.9 ml (SEM 0.21).

TABLE I. *Clinical patient data: mean maternal age, weight and dosage of drugs (±SEM). * Significant difference ($P < 0.05$)*

	Control thiopentone	Extradural bupivacaine
Age (yr)	27.7 (0.8)	25.5 (0.7)*
Weight (kg)	68.5 (1.9)	68.3 (1.5)
Drug dose (mg)	243.1 (7.2)	94.5 (1.0)

The mean times from induction (I–D), surgical incision (S–D) and uterine incision (U–D) to delivery and the average time to sustained respiration in the infants from birth (TSR) are in table II. The mean I–D interval was much longer ($P < 0.001$) with regional analgesia compared with general anaesthesia, but the average U–D intervals were similar. The infants initiated sustained respiration more rapidly after extradural blockade. Surgical incision to delivery intervals were not measured in the control series but, allowing 2–3 min for the induction of anaesthesia, were probably similar, on average, to those recorded in the extradural group.

There was no difference between the two groups with respect to the clinical status (Apgar minus

TABLE II. *Clinical data: time intervals (mean ± SEM).* † $P < 0.001$; * $0.1 > P > 0.05$

Interval	Thiopentone, $N_2O + O_2$, enflurane	Extradural, air + O_2
Induction to delivery (I–D) (min)	11.0 (0.7)	39.2 (2.4)†
Skin incision to delivery (S–D) (min)	Not timed	7.9 (0.7)
Uterine incision to delivery (U–D) (s)	71.2 (7.3)	83.4 (8.0)
Time to sustained respiration (TSR) (s)	27.3 (5.7)	14.3 (5.7)*

colour scores) of the infants studied. Two babies in each series failed to attain an A – C score (7 – 8)/8 2 min after delivery.

Three patients (9.4%) experienced some pain during the procedure, two (6.3%) requiring supplementation with analgesics after delivery of the fetus. A further six patients (18.8%) experienced mild discomfort during manipulation of the lower segment or placement of abdominal surgical packs. On subsequent questioning, six patients (18.8%) of the above nine stated they would prefer general anaesthesia for future operations. The remaining 26 (81.2%) were well satisfied with the regional technique. Surgical access to the uterus was satisfactory in all 32 patients.

The mean maternal blood-gas data of the two groups are shown in table III. Mothers receiving extradural bupivacaine were metabolically acidotic relative to the control group (greater mean [H+] and smaller average BE). The biochemical results from umbilical venous and arterial blood reflected those of the mother's blood (table IV). Mean maternal and fetal (Uv and Ua) P_{O_2} and haemoglobin oxygen saturation (S_{O_2}) were, as expected, less in the extradural series, reflecting the smaller $F_{I_{O_2}}$ inhaled by the mother in the extradural group (0.4 *v.* 0.5).

TABLE III. *Maternal blood-gas/acid–base status at delivery (mean ± SEM). Significant difference from "control":* * $P < 0.05$; *** $P < 0.001$

	Thiopentone, $N_2O + O_2$, enflurane	Extradural, air + O_2
$F_{I_{O_2}}$	0.5	0.4
[H+] (nmol litre^{-1})	39.1 (0.9)	42.7 (0.8)*
P_{CO_2} (kPa)	4.2 (0.1)	4.0 (0.08)
P_{O_2} (kPa)	23.1 (1.4)	20.2 (1.0)
BE (mmol litre^{-1})	−3.2 (0.5)	−6.7 (0.3)***

TABLE IV. *Umbilical venous and arterial blood-gas status at birth (mean ± SEM). Significant difference from "control":* * $P < 0.05$; ** $P < 0.01$; † $P < 0.005$; *** $P < 0.001$

		Thiopentone, $N_2O + O_2$, enflurane	Extradural, air + O_2
$F_{I_{O_2}}$		0.5	0.4
[H+] (nmol litre^{-1})	Uv	45.4 (1.2)	49.3 (0.8)**
	Ua	52.7 (1.6)	56.9 (1.3)*
P_{CO_2} (kPa)	Uv	5.4 (0.1)	5.3 (0.1)
	Ua	6.6 (0.1)	6.5 (0.2)
P_{O_2} (kPa)	Uv	4.3 (0.2)	3.5 (0.1)†
	Ua	2.5 (0.2)	1.9 (0.1)**
S_{O_2} (%)	Uv	71.9 (2.8)	58.7 (2.0)*
	Ua	4.0 (3.2)	20.7 (2.1)*
BE (mmol litre^{-1})	Uv	−3.7 (0.1)	−8.1 (0.4)***
	Ua	−6.4 (0.1)	−10.3 (0.5)***

Table V compares the maternal to fetal Δ(Ma – Uv)/Δ(Ma – Ua), and umbilical venous to arterial Δ(Uv – Ua) blood-gas tension differences of the two series. No statistically important differences were observed between the two groups.

TABLE V. *Maternal to fetal blood-gas difference at birth (mean ± SEM). (No differences were statistically significant)*

Differences	Thiopentone, $N_2O + O_2$, enflurane	Extradural, air + O_2
[H+] (nmol litre^{-1})		
Δ(Ma – Uv)	6.3 (0.8)	6.6 (0.5)
Δ(Ma – Ua)	13.7 (1.1)	14.2 (1.1)
Δ(Uv – Ua)	5.6 (0.5)	7.6 (0.8)
P_{CO_2} (kPa)		
Δ(Ma – Uv)	1.2 (0.1)	1.3 (0.1)
Δ(Ma – Ua)	2.3 (0.1)	2.5 (0.1)
Δ(Uv – Ua)	1.0 (0.1)	1.2 (0.1)
BE (mmol litre^{-1})		
Δ(Ma – Uv)	1.1 (0.5)	1.5 (0.2)
Δ(Ma – Ua)	4.2 (0.5)	3.7 (0.4)
Δ(Uv – Ua)	2.1 (0.3)	2.4 (0.4)

The correlation between the maternal (Ma) blood-gas and acid–base values and those obtained from the umbilical cord bloods (Uv and Ua), and between Ma and Δ(Ma – Uv)/Δ(Ma – Ua) are presented in table VI. Statistically important relationships were present in both groups between Ma and Uv/Ua, [H+], P_{CO_2} and BE. However, correlation

TABLE VI. *Correlation coefficients (r values): maternal arterial v. fetal (Uv and Ua) biochemical values and maternal to fetal Δ(Ma − Uv)/Δ(Ma − Ua), blood-gas differences. Statistically significant correlation:* * $P < 0.05$; ** $P < 0.01$; † $P < 0.005$; *** $P < 0.001$

Ma versus	Thiopentone	Extradural
$[H^+]$		
Uv	0.85***	0.76***
Ua	0.72***	0.53***
Δ(Ma − Uv)	0.42*	0.29
Δ(Ma − Ua)	0.54*	0.08
$P\text{co}_2$		
Uv	0.46**	0.71***
Ua	0.48**	0.65***
Δ(Ma − Uv)	0.46**	0.03
Δ(Ma − Ua)	0.56***	0.16
BE		
Uv	0.73***	0.84***
Ua	0.52†	0.56***
Δ(Ma − Uv)	−0.11	0.06
Δ(Ma − Ua)	−0.23	0.06

between Ma and Δ(Ma − Uv)/Δ(Ma − Ua)$[H^+]$ and $P\text{co}_2$ occurred only in the control series.

A significant correlation was demonstrable between I–D intervals and Uv/Ua acid–base status in the extradural series; $[H^+]$ was related directly and BE inversely to I–D intervals. In the control group, only Δ(Ma − Ua)BE increased in direct proportion to I–D interval (table VII).

Fetal acidaemia also increased significantly in the extradural series with lengthening of the U–D interval, a direct correlation being demonstrated between the U–D intervals and Ua$[H^+]$, Δ(Ma − Ua)$[H^+]$ and Δ(Ma − Ua)BE. Ua BE correlated inversely with the U–D interval (table VII).

No significant relationships could be demonstrated between the surgical incision to delivery (S–D) intervals and the Uv/Ua blood-gas and acid–base status or maternal to fetal acid–base differences in the extradural study.

Changes in mean maternal arterial systolic pressure and heart rate of the two patient groups, before the induction of anaesthesia and during the first 45 min of anaesthesia, are illustrated in figures 1 and 2. Both arterial systolic pressure and heart rate were, on average, significantly greater ($P < 0.001$) in the control group before induction and throughout the subsequent 45 min of anaesthesia when compared with the extradural series.

No significant changes in arterial systolic pressure were observed in either group when comparing the mean values before and after induction up to 45 min of anaesthesia (fig. 1). In contrast, the heart rate increased markedly in the first 10 min of anaesthesia in both series (fig. 2). This increase from the average pre-anaesthetic heart rate was sustained during both extradural and general anaesthesia for up to 40 min. However, the change was less pronounced between 10 and 40 min of anaesthetic time in the control series. Ten parturients developed significant hypotension (decrease in systolic pressure > 20 mm Hg), following extradural injection while lying on the left side before transfer to the operating table. In five patients receiving extradural analgesia the arterial pressure increased more than 20 mm Hg immediately following delivery, suggesting the presence of "concealed caval occlusion". Extradural blockade produced a

TABLE VII. *Correlation coefficients: (r values) time (I–D and U–D intervals) v. fetal biochemical status and maternal to fetal blood-gas tension differences at birth. Statistically significant differences:* * $P < 0.05$; ** $P < 0.01$; † $P < 0.005$. *(Thiopentone = "control")*

	Thiopentone			Extradural		
	$[H^+]$	$P\text{co}_2$	BE	$[H^+]$	$P\text{co}_2$	BE
I–D interval *v.*						
Uv	0.16	0.35	−0.23	0.39*	−0.11	−0.50†
Ua	0.27	0.32	−0.28	0.35*	−0.14	−0.44**
Δ(Ma − Uv)	0.20	0.35	0.24	−0.10	−0.08	−0.16
Δ(Ma − Ua)	0.33	0.25	0.45**	0.08	−0.13	0.03
U–D interval *v.*						
Uv	0.08	0.10	0.30	0.28	0.07	−0.21
Ua	0.18	0.16	0.21	0.53†	0.19	−0.49†
Δ(Ma − Uv)	0.12	0.09	−0.08	0.12	−0.01	0.24
Δ(Ma − Ua)	0.09	0.05	0.26	0.41**	0.16	0.51†

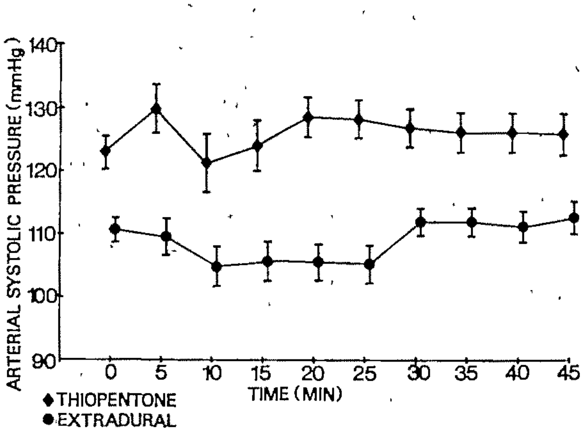

FIG. 1. Mean arterial systolic pressure (±SEM) (mm Hg) during the first 45 min of general anaesthesia (control group—thiopentone, 50% nitrous oxide in oxygen, 0.6% enflurane, myoneural blockade and IPPV) and regional analgesia (extradural bupivacaine 0.5% +1 in 200 000 adrenaline). A highly significant difference ($P < 0.001$) is present between the two series pre-induction (0 min) and throughout the 45 min of anaesthesia. However, no significant change from pre-induction mean systolic pressures at zero time was noted with anaesthesia in either group.

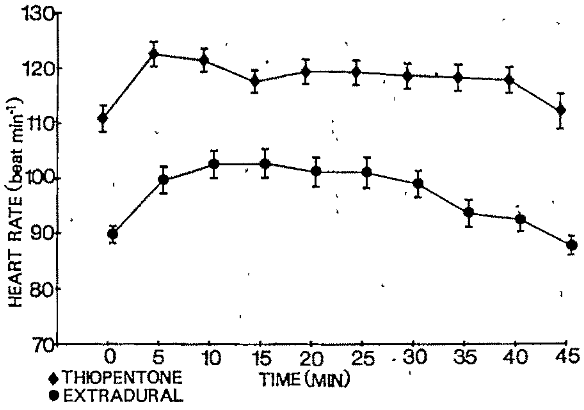

FIG. 2. Mean heart rates (±SEM) (beat min^{-1}), changes occurring within the first 45 min of general anaesthesia (thiopentone, 50% nitrous oxide in oxygen, 0.6% enflurane, myoneural blockade and IPPV) and regional analgesia. Highly significant difference ($P < 0.001$) present between the two series from pre-induction (0 min) throughout the 45 min of anaesthesia. Significant increase in mean heart rate from pre-induction values at zero time to 40 min of general anaesthesia and 30 min of regional blockade. The difference between mean heart rates before induction and 15–40 min after induction, although statistically significant in both series, was less pronounced with general anaesthesia, indicating a more gradual return to pre-induction values in the "control" group.

decrease in arterial systolic pressure to less than 80 mm Hg in only one mother, the hypotension being reversed by an infusion of fluid, change in posture and administration of a vasopresser according to the programme of study.

In contrast, in only two of the 30 patients receiving general anaesthesia did the arterial systolic pressure decrease significantly immediately following the induction of anaesthesia with thiopentone in the left tilt position (Buley et al., 1977). No patient in the control series showed evidence of "concealed caval occlusion", as suggested by a sudden and significant increase in systolic pressure immediately following the birth of the infant. The combined frequency of hypotension immediately following the induction of anaesthesia and relative hypotension before delivery (concealed aortocaval compression) was thus significantly greater in the extradural group (χ^2 with Yates correction = 10.64; $P < 0.005$).

DISCUSSION

Extradural analgesia for elective Caesarean section continues to gain in popularity. However, recent papers suggest that there is little to choose between general anaesthesia and extradural blockade for obstetric surgery with regard to their effects on fetal acid–base equilibrium (Belfrage et al., 1977; James et al., 1977; Palahniuk et al., 1977; Joupilla et al., 1978). In contrast, spinal subarachnoid block for diabetic mothers undergoing elective Caesarean section has been shown to increase the degree of metabolic acidosis present in the fetus in proportion to the degree of hypotension (Datta and Brown, 1977).

In the present study, surgery was conducted in the left lateral tilt position, after the initial use of the full left lateral posture in the anaesthetic induction room following extradural injection. Our results were compared with those from a previous investigation of patients similarly tilted but given a standard general anaesthetic (Buley et al., 1977). Mothers in both series received preloading with i.v. fluids to combat the effects of hypovolaemia as a result of overnight starvation and of pharmacologically induced vasodilatation.

However, the extradural group were at some disadvantage from the outset, in that the mothers inhaled a smaller concentration of oxygen (40% *v.* 50%) (Brownridge, 1978). This contrasts with the patients studied by James and his colleagues (1977), in whom mothers undergoing extradural analgesia inhaled pure oxygen and the general anaesthetic group only oxygen 66% in nitrous oxide.

The extradural group exhibited a significantly greater degree of metabolic acidaemia than the controls, which was reflected by the Uv and Ua[H^+] and Uv and Ua BE values. In addition, fetal oxygenation was inferior in the extradural group, presumably because of the smaller mean $F\text{I}_{O_2}$, which resulted in a lower average maternal Pa_{O_2}.

The greater concentration of fixed acids seen after extradural injection, which was proportional to the longer I–D intervals noted in the extradural series (39.2; SEM 2.4 *v.* 11.0; SEM 0.7), was presumably related to the smaller mean arterial pressures recorded with regional blockade, and the presence of concealed aortocaval occlusion in the small percentage of mothers preferring right rather than left lateral tilt (Buley et al., 1977).

Despite the relatively unfavourable maternal and fetal acid–base status of the extradural group, maternal to fetal blood-gas/acid–base differences in the present series were comparable to those of the control group. In addition, the clinical condition of the newborn infants was generally superior after extradural analgesia relative to general anaesthesia, in that respiration was sustained more rapidly.

These results accord with those of James and his co-workers (1977), who reported no difference in the maternal to fetal differences in two series of patients receiving either general anaesthesia or extradural blockade. These authors found also that the infants born under extradural block sustained respiration more rapidly than those delivered under general anaesthesia.

In this study, mean maternal arterial systolic pressure and heart rates both before induction and during anaesthesia were significantly less than those recorded previously with general anaesthesia (Buley et al., 1977). The greater mean systolic pressure and the relative tachycardia noted in the thiopentone group may reflect the fact that these patients received i.v. atropine before the induction of anaesthesia.

Arterial systolic pressures were maintained well throughout general anaesthesia with leftward tilt (fig. 1). Only two patients in the thiopentone series exhibited conversion of concealed to revealed aortocaval occlusion, as indicated by a decrease in arterial pressure immediately after the induction of anaesthesia, and none showed signs of concealed aortocaval obstruction, as demonstrated by a sudden increase in arterial systolic pressure after delivery of the fetus (Buley et al., 1977).

In contrast, although mean arterial systolic pressures were maintained well throughout extradural analgesia, albeit at a lower value than with general anaesthesia, 10 (31.3%) of the 32 mothers experienced significant decreases in arterial systolic pressure (> 20 mm Hg) shortly after the extradural injection. This occurred in patients lying in the full left lateral position before being moved to the operating table. One of these subjects required an injection of metaraminol in addition to the administration of i.v. fluids and a change in posture, to correct her hypotension which followed a too rapid extradural injection of bupivacaine. Furthermore, five mothers receiving an extradural injection exhibited a sudden and significant increase in systolic pressure immediately following delivery of the fetus, indicating the presence of concealed aortocaval occlusion, an increase which occurred despite omission of the usual single i.v. injection of Syntometrine given routinely after delivery under general anaesthesia. We applied the χ^2 test with Yates' correction to the overall frequency of hypotension after induction and relative hypotension immediately before delivery ($P < 0.05$).

Mean heart rates increased significantly from preinduction values in both groups. This increase was maintained for 30–40 min after the commencement of anaesthesia. Heart rates decreased towards preanaesthetic values more gradually with general anaesthesia.

Again our results accord with James and his colleagues (1977), who expressed concern at the degree of hypotension and tachycardia encountered during general anaesthesia for elective Caesarean section. Furthermore, five of their 15 "extradural" group required a vasopressor (ephedrine), because the arterial systolic pressure had decreased to less than 90 mm Hg. Presumably, even more meticulous attention to the avoidance of aortocaval compression by choosing the appropriate direction of lateral tilt and correction of hypovolaemia are required if maternal hypotension, as a cause of maternal metabolic acidosis, is to be eliminated.

In this study, we did not achieve quite the same high level (93.3%) of patient satisfaction with extradural analgesia as James and his colleagues (1977), 81.2% of our mothers receiving extradural injection were happy with the technique and a further 9.4% were satisfied, but expressed a wish to be asleep for future sections.

Thus, our findings lead us to the same conclusion as James and colleagues (1977), that no significant physiological advantage can, at present, be attributed to the use of extradural analgesia over general anaesthesia for elective Caesarean section. However, the importance of a lessened risk (with extradural block) of maternal death from pulmonary aspiration or failed intubation, and the psychological benefit to the awake mother who is fully involved in the birth of her child, cannot be over-emphasized.

We did not take advantage of the new neurobehavioural assessment scales which are available. These have been shown recently to offer a means of investigating the newborn, with respect to the neonatal effects of drugs used for obstetric analgesia and anaesthesia (Desmond, 1974). Assessment of neurobehavioural function may, in the future, allow more meaningful determination of the relative merits of regional versus general anaesthetic techniques for elective Caesarean section (Lund et al., 1977; Palahniuk et al., 1977; Hollmén et al., 1978).

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ANALGESIE EXTRADURALE POUR UNE OPERATION CESARIENNE: COMPARAISON AVEC L'ANESTHESIE GENERALE

RESUME

Trente-deux patientes ont reçu une anesthésie extradurale lombaire pour une opération césarienne à froid. Les résultats obtenus au cours de cette série d'opérations ont été comparés à ceux d'un groupe témoin similaire de parturientes, auxquelles on avait administré une anesthésie générale. Les mères et enfants du groupe extradural avaient une acidémie métabolique, par rapport aux témoins. Cependant les différences sang-gaz mères/enfants étaient comparables dans les deux séries. Les bébés ont soutenu la respiration plus rapidement après un blocage régional; autrement, l'état clinique des bébés a été similaire, que l'anesthésie ait été générale ou extradurale. Il n'est ressorti de cette étude aucun avantage de conduction par rapport à l'anesthésie générale, en ce qui concerne le statut biochimique du bébé à sa naissance.

EXTRADURALE ANALGESIE BEI KAISERSCHNITT: EIN VERGLEICH MIT ALLGEMEINER NARKOSE

ZUSAMMENFASSUNG

Zweiunddreissig Patientinnen erhielten lumbare extradurale Anästhesie für selbstgewählten Kaiserschnitt. Die Resultate dieser Serie wurden mit denen einer ähnlichen Kontrollgruppe unter allgemeiner Narkose verglichen. Die extradurale Gruppe von Müttern und Kindern war im Verhältnis zur Kontrollgruppe stoffwechselmässig azidämisch. Mütterlichfötale Blutgasunterschiede waren jedoch bei beiden Gruppen vergleichbar. Die Atmung trat bei Kindern nach regionaler Blockierung rascher regelmässig auf, ansonsten war der klinische Zustand der Kinder in beiden Gruppen ähnlich. Aus dieser Studie ergab sich kein Vorteil einer Leitwirkung gegenüber allgemeiner Narkose, was den biochemischen Status der Kinder bei der Geburt betraf.

ANALGESIA EXTRADURAL PARA SECCION CESAREA: UNA COMPARACION CON ANESTESIA GENERAL

SUMARIO

Treintidos madres recibieron anestesia extradural lumbar para sección cesárea electiva. Los resultados obtenidos de esta serie fueron comparados con los de un grupo de control semejante de parturientas que recibió anestesia

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SMALL ENDOTRACHEAL TUBES
Ventilator and intratracheal pressures during controlled ventilation

O. STENQVIST, H. SONANDER AND K. NILSSON

SUMMARY

The use of small endotracheal tubes reduces the trauma of intubation. Ventilator and tracheal pressures were measured during controlled ventilation with various tube dimensions and ventilation volumes. Ventilation with large volumes using small tracheal tubes results in high ventilator pressures. However, tracheal pressures are only marginally greater than those obtained with larger tubes. Small endotracheal tubes and high ventilation volumes result in a positive tracheal pressure at the end of expiration. The measured end-expiratory pressures are within the limits which might be used therapeutically (in PEEP). The force required to reshape endotracheal tubes of various dimensions to an "anatomical" shape was related to the tube dimensions; the beneficial effects of preformed, "anatomically shaped" endotracheal tubes can be achieved by using small tubes of standard design.

Endotracheal intubation can damage the upper airway at different anatomical levels, for example, the dorsal wall of the pharynx, the upper part of the larynx, the vocal cords, the subglottic region and the trachea itself (Bergström, 1962; Bryce, Briant and Pearson, 1968; Harrison and Tonkin, 1968; Lindholm, 1969; Hilding, 1971). Damage to the trachea, as caused by an inflated cuff, is a recognized problem and several techniques and designs of cuff have been devised to decrease the pressure exerted on the tracheal mucosa or the time for which pressure is applied (Carroll, McGinnis and Grenvik, 1974). Damage to the pharyngeal wall, the laryngeal entrance and the vocal cords is partly an effect of pressure and partly a result of the tube movement with erosion of mucosal surfaces.

Several authors have emphasized that tubes of smaller diameter cause less laryngeal damage (Bryce, Briant and Pearson, 1968; Harrison and Tonkin, 1968; Lindholm, 1969; Hilding, 1971; McGinnis et al., 1971; Goldberg and Pearson, 1972; Mathias and Wedley, 1974). Such tubes have two advantages—the intubation procedure is easier, and these tubes may require a smaller reshaping force to adapt them to the anatomical shape of the patient's airway.

The object of the present study was to determine if tubes of narrow bore could be used during controlled ventilation without there being marked resistance to inspiration or expiration. Also, we measured the forces necessary to reshape standard endotracheal tubes of various dimensions to conform to the anatomy of the upper airway.

METHODS

Ten patients with no known airway disease, undergoing minor e.n.t. operations, were studied before surgery. Informed consent was obtained from each patient. The mean age was 41 yr. Anaesthesia was induced with fentanyl 0.2 mg and thiopentone sodium 250 mg and maintained with nitrous oxide in oxygen (3 : 1). Ventilation was controlled via a non-rebreathing system and neuromuscular blockade was produced by the administration of pancuronium bromide 0.1 mg kg^{-1} body weight.

Ventilator and intratracheal pressures

Each patient was intubated sequentially with Shiley low-pressure cuff endotracheal tubes no. 5, 6, 7 and 8 (i.d. 5, 6, 7 and 8 mm, length 235, 278, 290 and 325 mm respectively). All tubes were used uncut and with the enclosed connector.

A polyethylene catheter (i.d. 1.2 mm) was applied to the outside of the endotracheal tube with its distal end in the trachea below the endotracheal tube and was used to measure the intratracheal pressure (transducer EMT 35, amplifier EMT 31, Siemens–Elema).

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Readings from the catheter were checked against a catheter-tip manometer (Millar PC 450). There was no damping and the time delay was found to be 0.1–0.15 s. In the experimental set-up a decrease in pressure of, at the most, 3 cm H_2O was measured from the ventilator manometer to the ventilator end of the endotracheal tube.

With each tube used, each patient was ventilated with a Servo-Ventilator 900 (Siemens–Elema) set at 8, 9, 10, 11, 12 and 13 litre min^{-1}. Other settings on the ventilator were: frequency 20 b.p.m., inspiratory time 25%, inspiratory pause 5%, square-wave inspiratory flow. The pressure and flow in the ventilator were measured continuously by the inbuilt pneumotachograph and plotted, with the intratracheal pressures, on an ink jet recorder (Mingograph 34, Siemens–Elema). The pressure transducers were calibrated against a mercury manometer, atmospheric pressure being taken as zero. Examples of the continuous curves of flow and pressure are shown in figure 1.

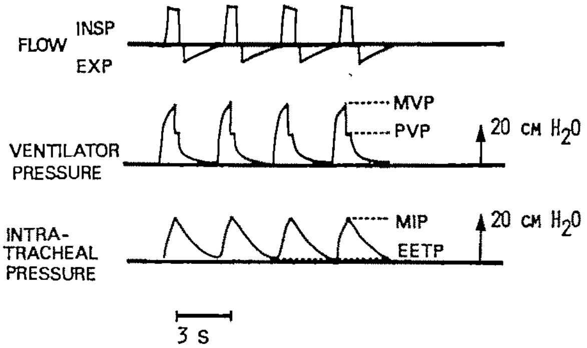

FIG. 1. Continuous display of flow and pressures during artificial ventilation, tube no. 9, ventilation volume 9 litre min^{-1}. MIP = maximal intratracheal pressure, MVP = maximal ventilator pressure, PVP = pause ventilator pressure, EETP = end-expiratory tracheal pressure.

From these recordings pressures were measured at four points: (1) maximum ventilator pressure (MVP); (2) maximum intratracheal pressure (MIP); (3) pause ventilator pressure (PVP), representing the pressure in the ventilator during the inspiratory pause; (4) end-expiratory tracheal pressure (EETP), representing the intratracheal pressure just before the next inspiration.

Reshaping of endotracheal tubes

Anatomically shaped endotracheal tubes have been devised by several workers (Dwyer, Kronenberg and Sakalad, 1949; Tashayod, 1967; Lindholm, 1969, 1973). Experimental studies of the force required to reshape various endotracheal tubes to an adequate form for the pharyngeal and laryngeal cavity have been presented previously (Lindholm, 1969; Lindholm and Carroll, 1975; Neuman, 1975). The force required to reshape endotracheal tubes to the contour of a Portex preformed endotracheal tube no. 8 was measured. The tubes were attached to a rack at the "oral" and "tracheal" ends and a peg used to simulate the base of the tongue. A load was attached to the tubes using a 20-mm broad strap with its centre 30 mm above the upper cuff margin (fig. 2). Loading was performed by filling a plastic bag with water until the curvature of the tube conformed to the model Portex preformed no. 8, whereafter the water in the bag was measured. Five measurements were made for each tube and five tubes of each brand and dimension were assessed.

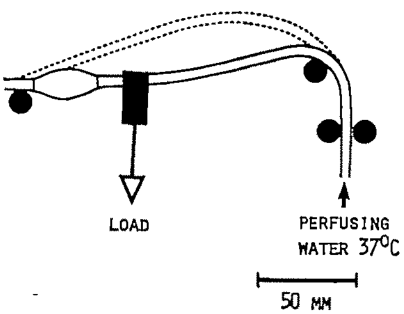

FIG. 2. Experimental design used to evaluate the force necessary to reshape standard tubes to the contour of a preformed tube (Portex). Dotted lines indicate the standard tube, continuous lines the same tube with applied force resulting in the desired shape. Black circles indicate fixed points in the set up. The load was always applied 30 mm "oral" to the upper margin of the cuff.

Portex Blue Line Murphy and Shiley low-pressure cuff Murphy no. 5, 6, 7, 8 and 9 were assessed. All measurements were made at a temperature of 36 ± 0.5 °C achieved by perfusing the tubes with water at 37 ± 0.1 °C.

RESULTS

Ventilator and intratracheal pressures

As the volume of ventilation was increased there were increases in MVP, the increase being more pronounced the smaller the tube used (fig. 3; table I). For example, MVP at a volume of ventilation of 13 litre min was 24 cm H_2O with tube no. 8 and 42 cm H_2O with tube no. 6. There was a corresponding but small increase in MIP as a function of the decrease in the diameter of the tube. MIP at a ventilation volume of 13 litre min^{-1} was 16 cm H_2O with tube no. 8 and 18 cm H_2O with tube no. 6.

TABLE I. *Pressures in the ventilator and trachea (cm H_2O) during artificial ventilation as a function of endotracheal tube size (i.d. mm) and ventilation volumes (litre min^{-1}), mean values and SD from* 10 *patients*

Tube size		Ventilation volumes (litre min^{-1}) 8	9	10	11	12	13
5	MVP	35±5	39±4	46±4	52±4	58±4	61±4
	PVP	10±2	11±2	13±2	14±2	16±2	17±2
	MIP	11±2	13±2	14±2	16±2	18±2	19±2
	EETP	1±1	2±1	3±1	4±2	6±2	6±2
6	MVP	23±3	26±3	30±2	35±3	38±3	42±3
	PVP	10±2	11±2	12±2	14±2	15±2	16±3
	MIP	11±2	13±2	14±2	15±2	17±2	18±2
	EETP	0±0	0±0	1±1	2±1	2±1	3±1
7	MVP	18±3	20±3	22±3	25±4	27±4	30±5
	PVP	10±2	11±2	12±2	13±2	14±2	15±2
	MIP	11±2	12±2	13±2	14±3	15±3	16±3
	EETP	0±0	0±0	0±0	0±0	1±1	1±1
8	MVP	14±2	17±3	19±3	21±4	23±4	24±4
	PVP	9±2	10±2	12±2	13±2	14±2	15±3
	MIP	11±3	12±2	13±3	14±3	15±3	16±3
	EETP	0±0	0±0	0±0	0±0	0±0	0±0

There was good agreement between the pressure developed in the ventilator during the inspiratory pause (PVP) and MIP. However, measured MIP was invariably 2–3 cm H_2O greater than PVP (fig. 3 and table I).

The end-expiratory tracheal pressure (EETP) was zero cm H_2O for all ventilation volumes with tube no. 8 and increased at volumes of ventilation greater than 11 litre min^{-1} with tube no. 7 and at 9 litre min^{-1} with tube no. 6. The highest EETP measured for tube no. 6 was 3 cm H_2O at 13 litre min^{-1} (fig. 3 and table I).

The difference between the maximal ventilator pressure and the maximal tracheal pressure (MVP − MIP) is an estimate of the pressure decrease across the length of the tube and is presented, as a function of the dimension of the tube and the volume of ventilation, in figure 4. The pressure decrease for a ventilation volume of 13 litre min^{-1} with tube no. 8 was about 8 cm H_2O and, for tube no. 6, 24 cm H_2O. The corresponding pressure decrease for a volume of 8 litre min^{-1} was 3 cm H_2O and 12 cm H_2O respectively.

Since the duration of inspiration was 25% of the cycle and the inspiratory flow was delivered as a square wave, the maximum flow was four times the set volume of ventilation as indicated within brackets

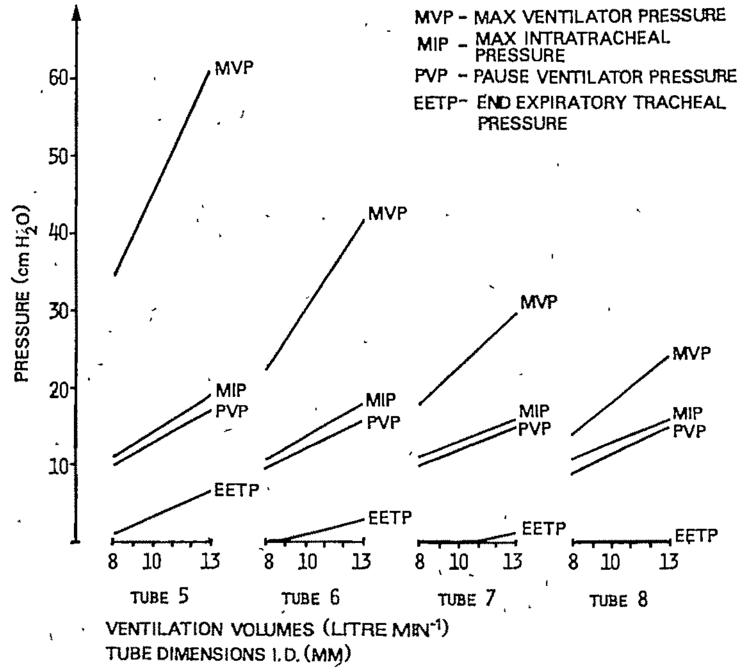

FIG. 3. Pressures in the ventilator and trachea during artificial ventilation as a function of endotracheal tube size and ventilation volumes, mean values from 10 patients for each tube dimension.

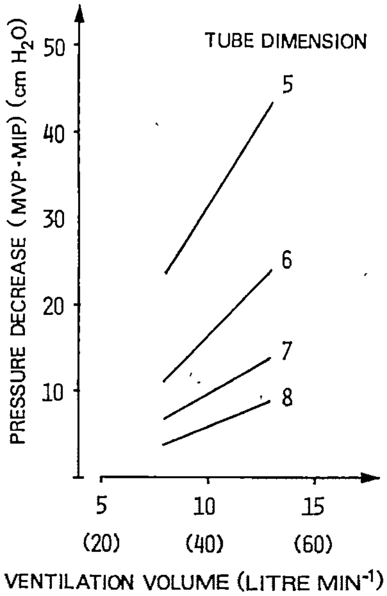

FIG. 4. Pressure decrease over endotracheal tubes of various sizes as a function of ventilation volumes. Values within brackets represent maximal flow during inspiration.

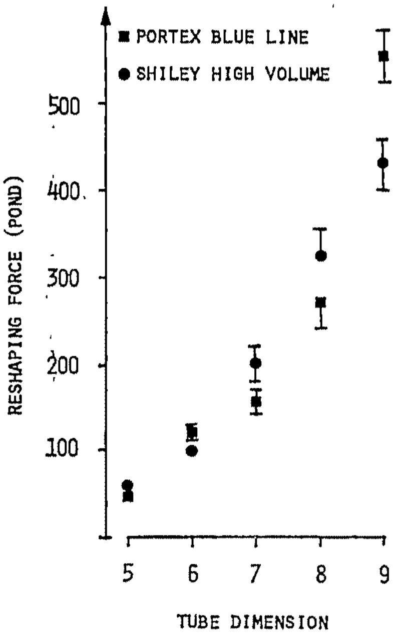

FIG. 5. Reshaping force for endotracheal tubes from two manufacturers as a function of tube dimension. Mean values ± SD from five tubes of each size. (1 pond = 0.0098 N.)

in figure 4. These maximum flow values should be used for comparison with measurements of the decreases in pressure over endotracheal tubes using a physical model with continuous flow (Orkin, Siegel and Rovenstine, 1954; Smith, 1961; Cave and Fletcher, 1968; Nunn, 1977).

Reshaping of endotracheal tubes

The force required to reshape the tube to the chosen "anatomical" design was greater for the larger tubes (fig. 5). It was found also that brands of tube studied differed in that the increase appeared to be "linear" for the Shiley tubes, whereas the increase was more "exponential" for the large Portex tubes. The force required to reshape the tubes was, for both makes of tube, more than twice as great for a no. 8 than for a no. 6 tube.

DISCUSSION

Pressure measurements

Whereas large volumes of ventilation result obviously in high MVP, high intratracheal pressures were not observed (MIP, fig. 3). The values recorded in this study were in agreement with information available from a similar investigation (Johansson and Löfström, 1975). High MVP as a result of high resistance in the endotracheal tube would, of course, influence artificial ventilation with any pressure-cycled ventilator (pressure generator), since the ventilator will not necessarily overcome the high resistance. The performance of the flow and time-cycled ventilator (flow generator) used for the present study was not influenced.

The small difference between MIP and PVP, MIP being consistently 2–3 cm H_2O greater than PVP, may be explained by the inertia of the combined patient–ventilator system. An inspiratory overshoot occurred after closure of the inspiratory valve on the ventilator as an effect of the inertia of the patient (thoracic wall and diaphragm with connected abdominal structures). This overshoot was followed by a small expiratory flow during the inspiratory pause as an effect of the elasticity of the lungs and thoracic walls. A rough calculation indicates that a displacement of an expiratory volume of less than 15 ml during the inspiratory pause would result in the measured MIP − PVP difference.

The increase in end-expiratory tracheal pressures (EETP, fig. 3) recorded with the narrow bore tubes was reached always within 10 respiratory cycles. During the initial respiratory cycles the resistance of the small tubes resulted in incomplete expiration during the time available. After a few cycles with ventilation at successively increasing FRC the elasticity of the lungs and the thoracic wall was sufficient to allow expiration of the inflated volume and no further increase in EETP occurred.

All pressure recordings were performed with standard length tubes. In the adult e.n.t. patient the no. 5 tube was about 3 cm too short whereas the no. 8 tube was about 4 cm too long for convenient handling. This influences the comparison of the pressure decrease across tubes of various dimensions (fig. 4).

The calculation of the pressure decrease presupposes that MVP and MIP occur simultaneously. With a ventilation volume of 13 litre min^{-1} through a no. 5 tube MIP occurs about 0.4 s after MVP. The real driving pressure (pressure decrease) over the tube can be estimated, from the original recordings, to be 5 cm H_2O greater than indicated by MVP$-$MIP in such a situation. This error is compensated for partially by the pressure decrease of about 3 cm H_2O in the ventilator tubing. The resistance of endotracheal tubes (pressure decrease/flow) increased slightly with an increasing flow rate. This can be expected in a system in which there may be a transition between laminar and turbulent flow. However, the increase in tube resistance over the flow range studied was moderate and linear, for example with tube no. 6 from 1.4 cm H_2O $litre^{-1}$ min at 8 litre min^{-1} ventilation volume to 1.8 cm H_2O $litre^{-1}$ min at 13 litre min^{-1} ventilation volume. Plotting the measured resistance of the tube as a function of the volume of ventilation indicated that the resistance throughout the flow range studied was mainly a resistance to laminar flow. Our results did not indicate a change to turbulent flow at the flow rates examined, nor did they indicate a transformation to turbulent flow even in small tubes at flow rates representing those in normal clinical use. A "critical" diameter of tube, as suggested by Nunn (1977), for various volumes of ventilation cannot be deduced from our results.

The use of small tubes involves the risk of occlusion and kinking. Our impression is that the use of endotracheal tube no. 6 during routine anaesthesia for adult patients does not result in an increased frequency of sudden or successive occlusion of the tube. Adequate humidification and a high flow rate through the narrow lumen of the tube seem to have abolished the problem.

Reshaping force

In our opinion the ideal endotracheal tube must be a compromise between adequate stiffness, allowing easy intubation, and a patent lumen and sufficient adaptability to the anatomy of the airway. The mechanical properties of modern materials used in endotracheal tubes are temperature-dependent. The reshaping force was 15–60% greater at a material temperature of 26 °C than at 36 °C and larger tubes were more temperature-dependent than the smaller ones. On the other hand, the reshaping force at 36 °C did not decrease after repeated "preformations" at 36 °C. The temperature dependence is an advantage as some of the stiffness necessary for the intubation is lost when the tube is in the airway.

Lindholm and Carroll (1975) presented reshaping values between 30 and 1000 ponds for tubes with 8 mm i.d.; Neuman (1975) gave values between 230 and 480 ponds for tubes with 10.2–11.5 mm o.d. The same authors transformed the measured reshaping force to a pressure by estimating a certain area of contact. It could be argued that a wider endotracheal tube offers a larger contact area resulting in a smaller pressure for the same reshaping force. If, arbitrarily, 20 mm of the tube length and half of the tube circumference is supposed to be in contact with the dorsal parts of the larynx, the resulting pressure load for various tubes can be calculated from our reshaping force (fig. 5). Approximate values would be 30 mm Hg for tube no. 6, 45 mm Hg for no. 7, 65 mm Hg for no. 8 and 90 mm Hg for no. 9.

CONCLUSION

Simultaneous measurements of the pressures in the trachea and the ventilator have shown high pressures at the oral end of the tubes at high volumes of ventilation when small endotracheal tubes were used. However, there were no corresponding increases of the pressure in the trachea during the inspiratory phase. Although the small endotracheal tubes resulted in a positive tracheal pressure at the end of expiration at high ventilation volumes, the measured end-expiratory pressure was, even in extreme situations, well within the limits of clinically applicable positive end-expiratory pressure. Endotracheal tubes with inner diameters of 6 or 7 mm can be used safely together with artificial ventilation by flow cycled ventilators (flow generators) during anaesthesia.

Anatomically shaped endotracheal tubes have been supposed to decrease the damage to the mucosal surfaces. The same beneficial effect can be achieved by using a small endotracheal tube, requiring a smaller reshaping force to conform to the anatomy of the airway. However, small endotracheal tubes require symmetrical high-volume, low-pressure cuffs and the length of the smaller tubes should be increased. The direct measurement of intratracheal pressure is valuable in all anaesthetic procedures, but especially when using small endotracheal tubes. An additional canal in the wall of the endotracheal tube, reaching the distal end, should be introduced in the manufacturing process.

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PETITS TUBES ENDOTRACHEAUX

Pressions ventilateur et endotrachéales pendant la ventilation contrôlée

RESUME

L'usage de petits tubes endotrachéaux diminue le traumatisme de l'intubation. La pression trachéale et celle du ventilateur ont été mesurées pendant la ventilation contrôlée en utilisant diverses dimensions de tubes et divers volumes de ventilation. La ventilation à l'aide de grands volumes par l'intermédiaire de petits tubes endotrachéaux entraîne de fortes pressions du ventilateur. Cependant, les pressions trachéales sont à peine plus fortes que celles obtenues avec des tubes plus larges. De petits tubes endotrachéaux et de forts volumes de ventilation entraînent une pression trachéale positive à la fin de l'expiration. Les pressions de fin d'expiration mesurées sont dans les limites que l'on peut utiliser thérapeutiquement (PEEP). La force requise pour modifier les tubes endotrachéaux des diverses dimensions et leur donner une forme "anatomique" a été liée aux dimensions des tubes; les effets bénéfiques des tubes endotrachéaux préformés "ayant une forme anatomique" peuvent être obtenus en utilisant de petits tubes de conception standard.

KLEINE ENDOTRACHEALRÖHREN

Ventilator und intratracheale Drucke bei kontrollierter Belüftung

ZUSAMMENFASSUNG

Die Verwendung kleiner endotrachealer Rohren verringert das Trauma der Intubation. Ventilator und trachealer Druck wurden gemessen bei kontrollierter Belüftung mit verschiedenen Rohrdimensionen und Belüftungsvolumen. Grossvolumige Ventilation mit kleinen Trachealrohren fuhrte zu hoheren Ventilatordrucken. Dagegen sind die trachealen Drucke nur geringfügig hoher als diese be grosseren Rohren. Kleine Endotrachealrohren und hohe Belüftungsvolumen fuhren zu einem positiven Trachealdruck am Ende der Ausatmung. Die gemessenen Endausatmungsdrucke liegen innerhalb der therapeutisch verwendbaren Grenzen fur PEEP. Die erforderliche Kraft zur Umformung endotrachealer Rohren verschiedener Abmessungen zu einer "anatomischen" Form stand im Verhältnis zu den Rohrenabmessungen; die vorteilhaften Wirkungen von vorgeformten, "anatomisch geformten" endotrachealen Röhren kann erzielt werden, indem kleine Rohren der Standardversion verwendet werden.

PEQUENOS TUBOS ENDOTRAQUEALES

Presiones del ventilador e intratraqueal durante ventilación controlada

SUMARIO

El empleo de tubos endotraqueales pequeños reduce el traumatismo de la intubación. Se midieron las presiones del ventilador y traqueal durante la ventilación controlada con diversas dimensiones de tubo y volumenes de ventilación. La ventilación con grandes volumenes utilizando tubos traqueales pequeños da por resultado elevadas presiones de ventilador. Sin embargo, las presiones traqueales son solo marginalmente superiores a las que se obtienen con los tubos de mayor tamaño. Los tubos endotraqueales pequeños dan como resultado una presión traqueal positive al final de la expiración y elevados volumenes de ventilación. Las presiones medidas al final expiratorio quedan dentro de los límites en que pueden ser empleadas terapéuticamente en PEEP. La fuerza necesaria para dar forma "anatómica" a los tubos endotraqueales de diveras dimensiones, se relacionó con la dimensión de los mismos; pueden obtenerse los efectos benéficos de los tubos endotraqueales preformados "anatómicamente formados", empleando tubos pequeños de diseño corriente.

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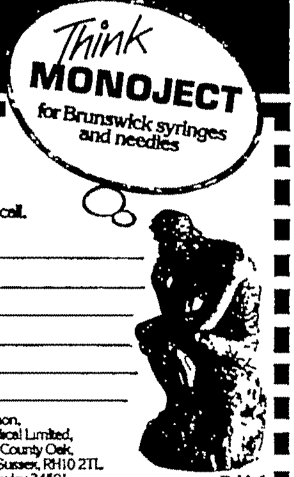
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Br. J. Anaesth. (1979), **51**, 383

CORRESPONDENCE

NITROUS OXIDE AND MAMMARY CARCINOMA

Sir,—In view of the favourable effect of nitrous oxide upon myeloid leukaemia (Eastwood et al., 1963) and lymphoma colony forming cells (Bruce, Lin and Bruce, 1970), we have examined the effect of nitrous oxide on mammary adenocarcinoma in mice.

After subcutaneous inoculation with tumour M8013 (mammary adenocarcinoma), one group of $C_{57}Bl_{10}$ mice was placed in one cage in a flow of nitrous oxide 80% and oxygen 20% which was passed for 11 of 13 consecutive days. A second identical group spent 11 of 13 consecutive days exposed to nitrous oxide 50% in oxygen, and a third identical group was kept in air (control group).

On the 13th day, the mice were weighed, the tumour diameters were measured and the leucocytes were counted (after bleeding to death). No effect of nitrous oxide 80% or 50% was observed on the growth of the tumours or on the leucocyte count in peripheral blood.

However, there was an obvious difference in loss of weight in the mice exposed to nitrous oxide, especially to the larger concentration (table I). Subsequently, we determined if nitrous oxide (mostly 80%) had any influence upon the effect of cytotoxic drugs. Mice with or without mammary adenocarcinoma M8013 were treated every 2nd day with one intraperitoneal injection of a cytotoxic drug—vincristine (Oncovin) 0.5 mg kg^{-1}, actinomycin D (Lyovac cosmogen) 0.06 mg kg^{-1} or cyclophosphamide (Endoxan) 50 mg kg^{-1}.

TABLE I. *Effect of nitrous oxide on $C_{57}Bl_{10}$ mice with mammary adenocarcinoma M8013 (mean values on the 13th day)*

Treatment	No. of animals	Tumour diam. (mm)	WBC count (10/ litre^{-9})	Wt (g)
Control	16	13.0	9.5	+1.4
N_2O 50%/ O_2 50%	16	14.5	12.1	−3.5
N_2O 80%/ O_2 20%	16	12.3	10.9	−7.7

The mice were allocated to three groups, placed in a cage with nitrous oxide, one 2 h before, the second simultaneously with, and the third group 2 h after the injection of the cytotoxic drug. The animals remained approximately 20 h in nitrous oxide (overnight until the next morning). In most of these experiments, the combined therapy produced more weight loss and a higher mortality rate than nitrous oxide alone. The tumours of these mice were the same size as those in mice treated only with cytotoxic drugs, suggesting that nitrous oxide in combination with cytotoxic drugs did not influence M8013 mammary adenocarcinoma in $C_{57}Bl_{10}$ mice.

If atropine 0.5 mg kg^{-1} or atropine 0.5 mg kg^{-1} with promethazine 1.6 mg kg^{-1} or atropine 0.5 mg kg^{-1} with propranolol 1.6 mg kg^{-1} were administered i.v. just before placing the animals in nitrous oxide, there was less weight loss and a smaller mortality but no effect on the tumours, in comparison with mice treated with cytotoxic drug and nitrous oxide.

We conclude that the administration of nitrous oxide had no inhibitory effect on the growth of M8013 tumours in mice either alone or in combination with cytotoxic drugs.

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ETHICAL PROBLEMS IN INTENSIVE CARE

Sir,—I would like to reply to Dr Searle's (1978) comments about my paper (Bishop, 1978).

By definition, any essay is sketchy and I would remind Dr Searle that the "anecdotal evidence" was based not only on my own experience, but also on that quoted in the references given.

I would also point out that his own evidence is anecdotal; this is understandable since politically delicate matters are rarely reported and what may be difficult for doctors to collect is impossible for nurses. Furthermore, the fact that evidence is anecdotal does not necessarily render it irrelevant.

While it would appear that an excellent interdisciplinary relationship between consultants in his hospital avoids the not infrequent dispute over treatment of the critically ill patient, Dr Searle must admit that such a relationship is not universal.

On the question of keeping terminal patients in an Intensive Care Unit, I do query the justification of blocking a highly specialized bed required by a patient with greater needs. I fully appreciate the psychological difficulties for both the relatives and the staff in this situation, which is why I personally advocate extension units to Intensive Care Units with beds unsupported by extensive monitoring equipment, and which require a lower ratio of staff.

It is reassuring to find that Dr Searle agrees that there is no place for pride or prejudice in making decisions on the subject under discussion. The fact that general acceptance of the indications for such decisions is difficult to achieve is no reason for not trying.

V. A. Bishop
London

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EXTRADURAL ANALGESIA REVISITED

Sir,—I was interested to read the article by Dr Grundy and his colleagues (1978) on extradural analgesia, but I find some of their data and conclusions surprising. The authors used bupivacaine 0.75% in volumes of 10–20 ml in a series of 344 patients. No other analgesic drugs were tested and the subjects' ages were in the range 16–86 yr.

In no instance did the authors observe any cephalad spread of analgesia beyond dermatome T2. I find this astonishing in such a large series where large doses were used, and this apparent lack of upward spread is not in accordance with my own experience or that of others. Reviewing a relatively small series of extradural blocks performed at L2/3 with bupivacaine 0.75% given in the sitting position, I found that two patients of 68 experienced spread of analgesia beyond T2. One 44-yr-old patient received 0.75% bupivacaine 18 ml and analgesia spread to T1; another aged 43 yr received 20 ml and analgesia spread to include C8. Dr Nigel Sharrock (1977), who is quoted by the authors, gave 40 patients only 10 ml of 0.75% bupivacaine and found a spread to T1 in one patient. Dr Grundy and his colleagues acknowledge the help given by their residents-in-training in collecting their data, and without being in any way critical, I wonder if this may explain the nature of the data that has been presented, and the limited upward spread of analgesia that the authors seem to have observed in their elderly patients.

Anyone who has attempted to assemble accurate statistics on the dermatome spread of sensory anaesthesia knows the pitfalls. It takes a long period of training and observation and a compulsive degree of attention to detail to obtain precisely identical findings among a small group of observers, and the chances of between-observer error increases greatly as the group enlarges. Could it be that the observer group was enlarged to a point where such an error became significant?

In attempting to explain the apparent freedom from spread beyond T2, the authors postulated an anatomical barrier in the cervico-thoracic region of the extradural space. I know of no clinical, radiological or anatomical evidence to support the contention that fluid spreads with difficulty above the T2 extradural space in the living subject. Certainly, fluids pass relatively easily from the intervertebral foramina in the cervico-thoracic region, but that does not dictate that the cause is a block to axial flow. Segmental mid- and upper-thoracic blocks frequently spread to involve the lower cervical segments unless care is taken to limit the dose injected. In dogs, also, radiological experiments with metrizamide have shown unimpeded flow between the thoracic and cervical regions of the extradural space (Bromage et al., 1978).

The authors looked for, but did not find, an increased segmental spread in the arteriosclerotic subjects, and they quote Dr Sharrock's article of 1977 to support their own findings. Unfortunately, neither their own data nor that of Dr Sharrock show evidence that their observations were carried on long enough to detect complete spread of analgesia. One of the features of the spread of lignocaine in arteriosclerotic subjects is unusual slowness (Bromage, 1962a). The observer may have to wait for 30 min or more before spread is complete. Sharrock's measurements were completed in only "20 to 30 minutes" and so may well have missed some extremes of spread. Grundy and his colleagues did not comment on the duration of observations and it is possible that between-observer error and dermatome onset profiles of less than 30 min may have led to an underestimate of the true degree of segmental spread.

With regard to their linear regression data: in several of the figures, linear regression lines of spread and age are extrapolated well beyond the limits of the data and this is misleading and statistically unacceptable.

Finally, the authors claim to have refuted an early schema of mine (Bromage, 1962b) expressing a direct volume-spread relationship in extradural blockade. That schema is admittedly an approximation (Bromage, 1978), and since our isotope work of 1963 (Bromage, Joyal and Binney, 1963) it has not been assumed to represent an homogeneous uptake of local anaesthetic within the spinal canal. However, it has been a useful model if only to make anaesthetists aware of the potential danger of using excessively large doses of drugs. The authors do seem to appreciate this lesson, as shown by the uneven selection of their dose groups. It is commendable that they injected a volume of 0.75% bupivacaine 20 ml in only one patient older than 70 yr, whereas they did not hesitate to use smaller volumes in 32 patients aged 70–86 yr—a difference that is considerably greater than can be attributed to chance.

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Sir,—We hope we can reassure Dr Bromage. Our residents performed many of the extradural blocks, but the blocks were performed under close supervision and the levels of anaesthesia achieved were checked, mostly by one of the three principal authors. The timing of this check was usually 20–40 min after injection, and those patients studied during operation and into the recovery period showed no late progression of anaesthesia. Initially, we also were surprised by the consistency of perineal anaesthesia and the relatively small spread of values for the upper level of anaesthesia. We sought actively evidence of anaesthesia in the arms wherever there was a likelihood of a high level of anaesthesia and latterly we used 10-ml injections in young patients undergoing perineal surgery with complete success. We do not think that we missed a slow spread to a high level of anaesthesia, or that our observer group was large enough to distort our data. Dr Bromage's experience with patients in the "sitting position" appears to support the literature which indicates that a higher level of anaesthesia may be produced in this position (Nishimura, Kitahara and Kusakabe, 1959).

We suggested that the described narrowing of the extradural space from the thoracic to the cervical region (Cheng, 1963) produces impedance to cephalad flow such that spillage from the lateral intervertebral foramina occurs in preference to further cephalad flow to the cervical extradural space. This is supported by radiological studies in cadavers (Moore et al., 1957), but not by studyies in dogs (Bromage et al., 1978). We are also impressed by the rarity of "high extradurals" in clinical practice despite the use of 25–35 ml routinely by some anaesthetists. We postulated no anatomical barrier, but wonder if our suggestion of a functional impedance represents a "safety valve" in the presence of unnecessarily large volumes of local anaesthetic. This safety mechanism would, of course, be lost where flow out of the thoracic lateral intervertebral foramina is impaired.

Dr Bromage's contributions to extradural anaesthesia are universally acclaimed and his schema for computation of volume requirements has gained wide clinical acceptance. However, our results show that the volume necessary for extradural analgesia is not as critical as his schema suggests and that the initial assumption for his schema should be reconsidered.

E. M. GRUNDY
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EFFECT OF REPEATED ADMINISTRATION OF SUBANAESTHETIC CONCENTRATIONS OF ETHER AND HALOTHANE ON THE RAT

Sir,—Experimental studies of the effects of chronic exposure to inhalation anaesthetics are few. A study is described demonstrating the effect on the rat of repeated administration of subanaesthetic concentrations of ether and halothane.

Ether 4% and halothane 0.5% in air were administered to rats of either sex for 15 min per day, 6 days per week for 3 months. A control group breathed air only. The occurrence and outcome of pregnancy and the presence of histopathological changes were noted.

In both ether and halothane groups, there was an initial decrease in weight during the 1st week, followed by a gradual increase reaching that of the control group. None of the females of the halothane group became pregnant. Only one female in the ether group became pregnant, during the 3rd month, and delivered nine offspring; eight died during the first 24 h and the ninth after 48 h. Table I shows the weight and the crown–rump length of the litters in the control and ether groups. The mean litter weight was 3.8 ± 0.3 g in the ether group and 4.9 ± 0.4 g in the control group ($t = 7.432$, $P < 0.001$). The crown–rump length averaged 43 ± 1.0 mm in the control group and 41 ± 5.0 mm in the treated animals ($t = 1.754$, $P > 0.05$). All the offspring of the mother in the ether group had cardiomegaly.

TABLE I. *Mean weight and mean crown–rump length of the offspring in the control and ether groups. Each group comprised four females*

	Pregnant mothers	Offspring		
		No.	Wt.(g)	Length(mm)
Control	3	20	4.9 ± 0.4	43 ± 1
Ether	1	9	3.8 ± 0.3	41 ± 5

After exposure to either anaesthetic there was congestion of the liver, spleen, kidney and lungs. Moderate degenerative changes were present, such as cloudy swelling and fatty change of the liver, cloudy swelling of the proximal convoluted tubules of the kidney and destructive changes in the alveoli of the lungs. Other organs such as the heart, testicles and brain appeared to be normal.

The concentrations used in this study were greater than those used in previous studies (Chenoweth et al., 1972), to magnify the possible toxicological effects of chronic exposure.

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REFERENCE

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THE LOWER OESOPHAGEAL SPHINCTER AND REGURGITATION

Sir,—We have recently read the editorial by Dr Scott (1978) relating to Mendelson's Syndrome. He does not mention recent work to show that anaesthetic drugs adversely effect lower oesophageal sphincter (LOS) tone (Lind, Crispin and McIver, 1968; Hall et al., 1975; Brock-Utne et al., 1978b). Theoretically, regurgitation of acid gastric content into the oesophagus can result from one of three basic causes (Marchand, 1955), namely a decrease in LOS tone, an increase in intragastric pressure above that resisted normally by the resting LOS and mechanical factors which are now thought to be of little consequence (Mann, Greenwood and Ellis, 1964). A correlation between reflux and decreased LOS pressure has been reported (Haddad, 1970). Hence a "good" sphincter will prevent gastro-oesophageal reflux. In contrast, a "poor" or "weak" sphincter will fail in this regard. This concept is not universally accepted because considerable individual variation in resting sphincter tone has been reported (Skinner and Camp, 1968). However, a zone of increased intraluminal pressure does exist at the gastro-oesophageal junction and acts as a physiological sphincter (Cohen and Harris, 1971). Any drug which decreases the sphincter tone will therefore increase the chances of regurgitation and pulmonary aspiration.

Atropine (Dow et al., 1978), glycopyrrolate (Baraka et al., 1977) and hyoscine (Crawford, 1972) have all been recommended in obstetric anaesthesia. However, all three drugs reduce LOS tone (Lind, Crispin and McIver, 1968; Brock-Utne et al., 1976, 1977, 1978c). Metoclopramide 10 mg counteracts the deleterious effects of atropine (Brock-Utne et al., 1976). It has been our practice for many years to give these two drugs i.v. simultaneously before induction at Caesarean section. We now give metoclopramide i.v. by itself, 5–10 min before atropine, as suggested by Laitinen and colleagues (1978). They have found that when metoclopramide is given first, subsequent administration of atropine does not alter LOS pressure. Despite the fact that this work was performed in dogs, it is relevant information for the obstetric anaesthetist and at present we are repeating this work in humans.

Regurgitation and inhalation of acid gastric content remain major hazards in the recovery phase after general anaesthesia. Therefore the effect of atropine and neostigmine, given at the end of a general anaesthetic, on LOS tone is also relevant. We have found that when using the greater dose of neostigmine (5 mg) there is a significant increase in the LOS pressure by 1.4 kPa ($P < 0.001$) (Brock-Utne et al., 1978a). This compares favourably with atropine 1.2 mg and neostigmine 2.5 mg which decreased the LOS tone insignificantly by a mean of 0.7 kPa ($P < 0.1$) (Brock-Utne et al., 1978a). The former dosage of this drug combination therefore appears preferable in patients presenting for emergency surgery if the integrity of the lower oesophageal sphincter is to be maintained during extubation and recovery from general anaesthesia. The same changes are seen when glycopyrrolate is used instead of atropine (unpublished data).

Finally, on the rationale of Laitinen's work, pertaining to the drug interaction of atropine and metoclopramide, what will the effects be on the LOS if atropine is given before neostigmine for reversal of neuromuscular blockade, a common practice amongst many anaesthetists?

We endorse the warning which Dr Scott gives regarding complacency towards Mendelson's Syndrome which is now a major cause of maternal death relative to other factors, the importance of which has declined over the past 10 years.

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Br. J. Anaesth. (1979), **51**, 387

BOOK REVIEWS

Anaesthesia for Cardiac Surgery and Allied Procedures. By Margaret A. Branthwaite. Published by Blackwell Scientific Publications, Oxford. Pp. 193; illustrated, indexed. Price £8.25.

This book is aimed, as the author states, at those who are faced with the practical aspects of anaesthesia for cardiac surgery for the first time, and at those who are preparing for postgraduate examinations. Of its 10 chapters the first seven progress in logical sequence. The opening chapter is a rather short treatment of applied physiology and a little more information would be welcome, for example on the biochemical, metabolic and hormonal aspects of cardiac function, especially as these relate to the damaged heart and the post-perfusion period of open heart surgery.

There follow excellent chapters on the medical and surgical aspects of heart disease, the techniques of investigation and operative treatment, and of anaesthetic management, in both congenital and acquired heart disease in adults. Next, a chapter is devoted to extracorporeal circulation and the methods of protecting the myocardium during surgery; there is a separate chapter on anaesthesia for cardiac surgery during the first year of life.

Again and again, as one reads the concise and unambiguous text, one finds descriptions of particular aspects of surgical technique and of special features of disease, or of the consequences of clinical practice which are of immense value to the practising anaesthetist, and which speak volumes for the knowledge and experience of the author.

The chapters are headed by a full listing of the topics covered within, and an important feature of the book is the way in which each chapter is followed by an extensive but carefully selected list of references conveniently arranged by subject and often further divided under subsidiary headings. This extends the usefulness of the book so that, to the serious student and the more experienced anaesthetist, it becomes a valuable guide to recent literature, although it is not a complete source book. The text is well set out on a matt paper and nine pages of index lead the reader directly to most topics of interest.

The diagrams and half-tone illustrations are, for the most part, well chosen and sufficient for their purpose, although some further illustration of described surgical procedures would be helpful. The chapter on "Extracorporeal Circulation" would also benefit from a photograph of a fully assembled machine, and further examples of bubble and disposable membrane oxygenators, to indicate the "state of the art". However, these are peripheral considerations. It is the text which makes this a book strongly to be recommended to its intended readership and beyond. The clinical chapters are admirably complete, with one exception: there is no chapter dealing specifically with postoperative cardiac intensive care, which is an important part of the anaesthetist's field of interest. At the end of the last chapter on "Complications of Heart Surgery" Dr Branthwaite refers the reader to a book on "Postoperative Cardiac Intensive Care" of which she is joint author. This is understandable, but the present volume would benefit immeasurably from a modest expansion of the last chapter to contain a statement of clinical practice in the postoperative ward as satisfying as the chapters which go before.

Fortunately, this book is otherwise pleasing and deals with a subject which is still changing rapidly, so that the opportunity will surely soon arise for a second edition in which to remedy this omission. Let us hope the opportunity is taken—it will be well worth the inevitable extra cost.

M. D. Hargreaves

Clinical Anesthesia. Procedures of the Massachusetts General Hospital. By Philip W. Lebowitz. Published (paperback) by Little, Brown & Co., Massachusetts. Pp. 437; indexed; illustrated. Price U.S. $5.47.

This manual has been prepared by members of staff of the Department of Anesthesia at the Massachusetts General Hospital and gives detailed guidance on a wide range of the anaesthetist's duties: evaluation before operation, techniques of general and regional anaesthesia, anaesthesia in special situations, such as cardiac surgery, obstetrics and paediatric surgery, the control of arterial pressure, the problems of anaesthesia in the presence of disease of the heart, kidney and liver, and the complications of anaesthesia. The last two chapters deal with aspects of intensive care medicine. Because the book has a strong North American flavour, in the use of drug names for example, its full potential cannot be realized in a country such as the United Kingdom. With pencilled editing, however, it would be a most valuable addition to the working books of an anaesthetic department. Not least among its attractive features is the modest price.

Alastair A. Spence

Pulmonary Pathophysiology—The Essentials. By John B. West. Published (paperback) by Blackwell Scientific Publications, Oxford. Pp. 227; illustrated; indexed. Price £7·50.

This paperback is the companion volume to *Respiratory Physiology—The Essentials* by the same author and is also designed primarily for medical students. The book is divided into four sections: Lung Function Tests, Function of the Diseased Lung, Function of the Failing Lung and Short Appendices which occupy 18 pages and provide a glossary of symbols, a short list of references, suggestions for further reading and a list of questions and answers. Although the third section, devoted to respiratory failure, oxygen therapy and mechanical ventilation, would appear elementary to anaesthetists, there is much in the first two sections which could be read profitably by such specialists for both examination or refresher purposes.

Overall, this text represents a superb example of bridging the gap which is commonly present between the basic science of the pre-clinical curriculum and the undergraduate clinical courses in medicine. One can only hope that all medical students will be encouraged to acquaint themselves with it and profit by such an experience with the same sense of enjoyment as the reviewer.

Graham Smith

Principles and Practice of Obstetric Anaesthesia. By J. S. Crawford. Published (1978) by Blackwell Scientific Publications. Pp. 392; illustrated; indexed. Price £18.75.

The first edition of this book established the author's scholarly approach: a broad scrutiny of the literature and constant questioning of established "fact". The subsequent editions, with his original contributions, have had a major influence on obstetric anaesthetic practice. In the 5 years since the last edition there have been important advances in obstetric analgesia and anaesthesia, and this edition (completed during 1977) reflects the growth, being one-third longer and with a reference list twice as long.

Chapter I (The Mother) now includes a full and informative description of the value of partography, but there is a less complete account of fetal monitoring. Pre-eclamptic toxaemia and the pathology of other diseases are dealt with in great detail. There is a helpful discussion on the choice between ergometrine and syntocinon.

Chapter II (Placental Physiology) and Chapter III (The Placenta, Drugs and the Fetus) are difficult subjects, which are generally well managed. Dr Crawford correctly emphasizes the importance of rigid criteria for maternal selection when studying the effects of drugs upon the fetus. The description of placental transfer of drugs is too compressed, and without illustration.

Chapter IV (Analgesia for Labour and Vaginal Delivery) fulfils expectations of sound practical advice which would be expected from such an experienced source. Dr O'Driscoll's views are presented fairly on the importance of sympathetic and personal management of the mother in labour in reducing the need for drugs, while Dr Crawford remains convinced that labour is a painful process for most women. There is a full description of the technique of extradural block as practised in Birmingham, with sound commentaries on complications. It is emphasized that if a midwife is allowed to "top up", then the medical attendant must still be immediately available to be called to the delivery suite. There are briefer accounts of other methods of pain relief used in labour.

Chapter V (Caesarean Section) includes the many important contributions of Dr Crawford in this field. In Chapter VI (Other Considerations of Obstetric Practice) pre-eclamptic toxaemia and eclampsia are discussed fully, but tachycardia from hydrallazine would not be "treated with practolol *and* diazoxide" (my italics), and not many clinicians would now administer diazepam in the total dose recommended.

In Chapter VII (The Child) levallorphan is still advocated, since the author considers that naloxone has a too short duration of action. However, i.v. naloxone can be repeated or administered i.m. in a larger dose.

The book is essential reading for every anaesthetist, obstetrician and neonatologist concerned with pregnancy and delivery. However, there are blemishes. It is not a book to dip into, but requires a great deal of concentrated thought from the reader. This is mainly because the text has few sub-headings, the illustrations are too few and generally of a poor standard, and the index is inadequate. This edition, however, bears the imprint of many years' experience, and there are few aspects which do not receive scrupulous attention, and often light, but firm popping of bubbles of pomposity or ignorance. The book opens with a quotation from St Augustine, "The greatest evil is physical pain". Dr Crawford has once again contributed enormously to reducing this affliction in obstetrics. Undoubtedly the "Birmingham Bible" will help many a young anaesthetist to appreciate the problems unsolved of obstetric anaesthesia and analgesia.

M. Rosen

Zoo and Wild Animal Medicine. By Murray A. Fowler. Published (1978) by W. B. Saunders Co., Eastbourne. Pp. 951; illustrated; indexed.

This text covers a wide range of prevention, diagnosis and treatment of disease in many species. Included in the text are detailed and usefully illustrated accounts of anaesthesia of a wide range of creatures from primates and reptiles to perching birds and vampire bats.

Introduction to the Practice of Anesthesia. Editors M. Lichtiger and F. Moya, 2nd edn. Published by Harper and Row, New York. Pp. 586; illustrated. Price $27.50.

The novice in anaesthesia is faced with the dilemma of acquiring a highly detailed theoretical understanding of the scientific foundation of the specialty at the same time as a practical familiarity with the subject to enable him to function as an anaesthetist. To this latter purpose, a view of the whole breadth of the specialty is required. The larger standard textbooks on the U.K. market are too detailed to paint such a broad canvas rapidly, whilst texts aimed at the undergraduate are often too insubstantial. For the U.S. resident, however, this gap is bridged splendidly by *Introduction to the Practice of Anesthesia.*

This text represents the collective wisdom of 39 contributors, past or present Faculty of the University of Miami, distilled into 41 chapters. Each chapter is quite brief, didactic in style and dogmatic in approach—the teacher writing briefly on a specific topic produces both what is important and also what is patently his own practical experience. Bearing in mind the student for whom this is intended, the unsubstantiated statements inherent in this approach are not irritatingly obtrusive, while the relatively brief treatment of specific topics tends to accentuate principles rather than idiosyncrasies of technique. Other problems inherent in the multi-author approach may also be found, but are not too disconcerting: for example, lack of balance is exemplified by induced hypothermia occupying twice the space taken by induced hypotension.

The second edition of this text differs from the first by updating of several chapters and the addition of new chapters on cardiopulmonary bypass, resuscitation, pharmacodynamics of volatile agents and respiratory therapy. In addition, the format has been improved considerably by the use of heavier type for subheadings and many diagrams have been improved. In general, diagrams are excellent and used liberally, but the occasional presence of cartoons remains a matter of personal taste.

This book fulfils its designated function admirably. Although there is an accent on American techniques, drugs and equipment, there is much which is appropriate for those commencing a career in anaesthetics outside the U.S.A.

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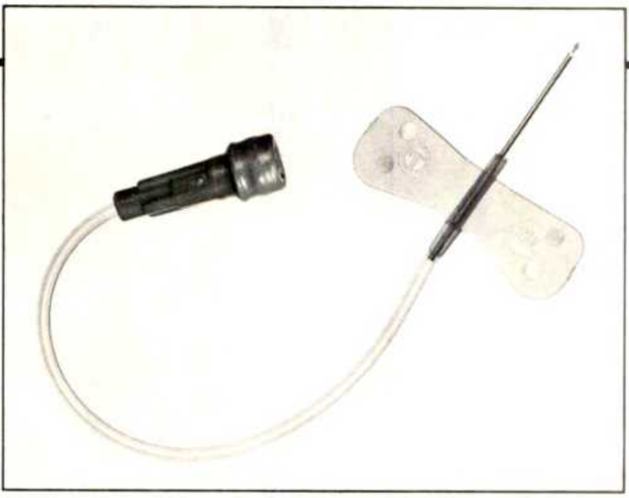

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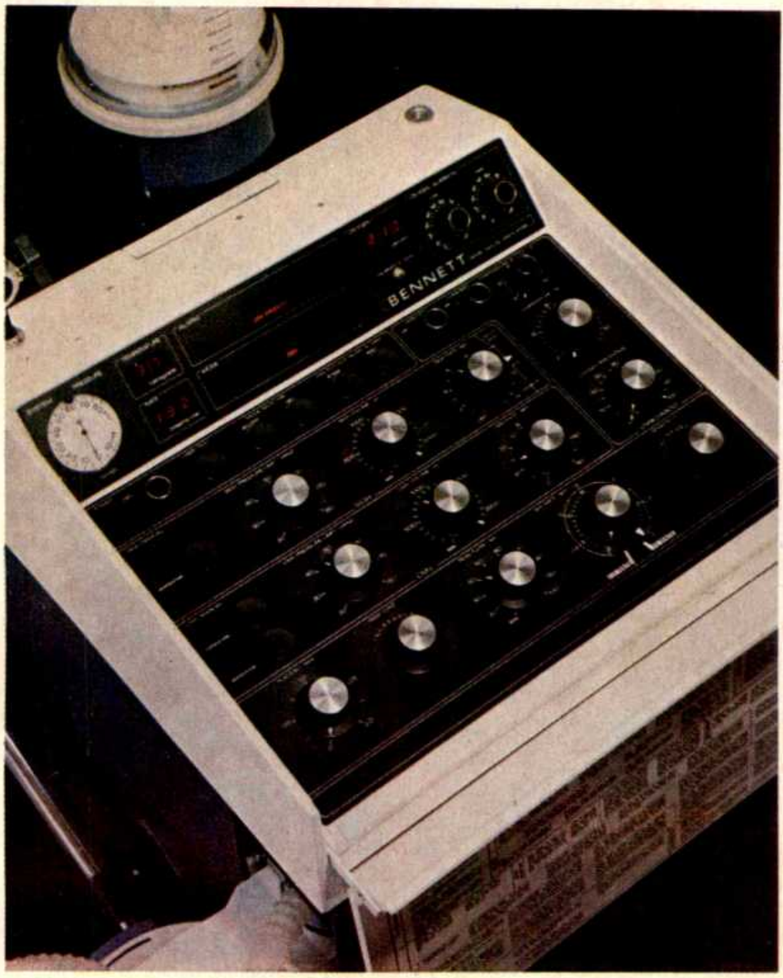

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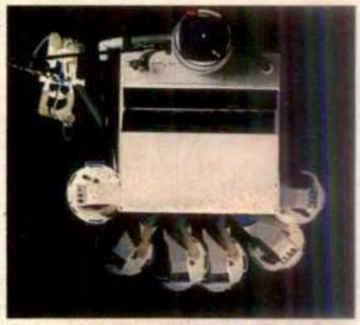

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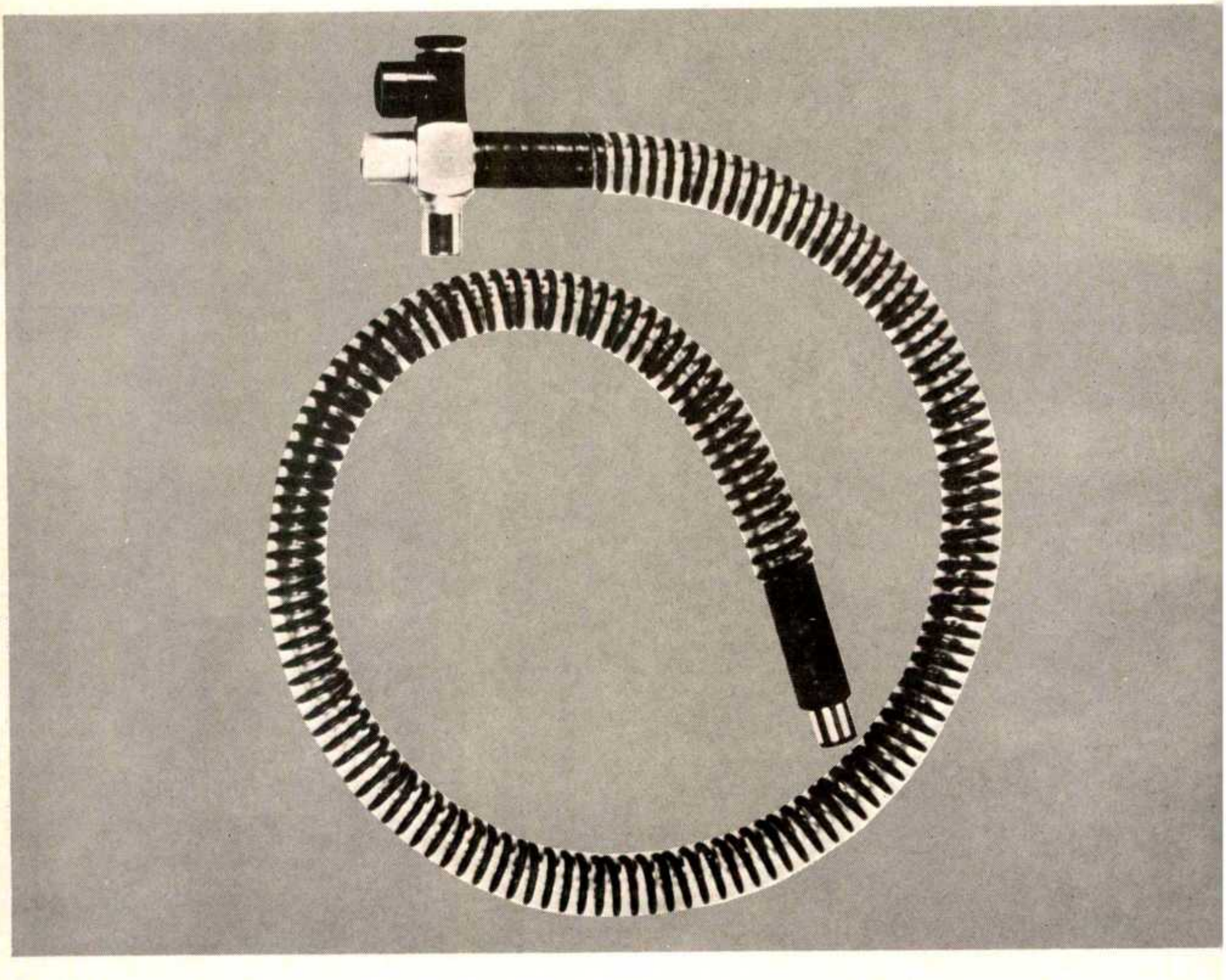

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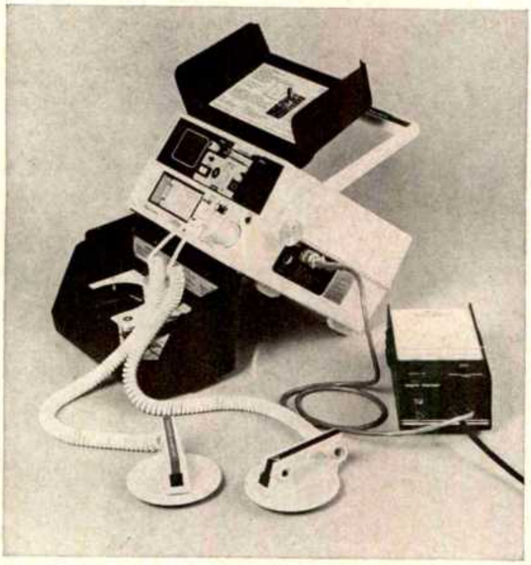

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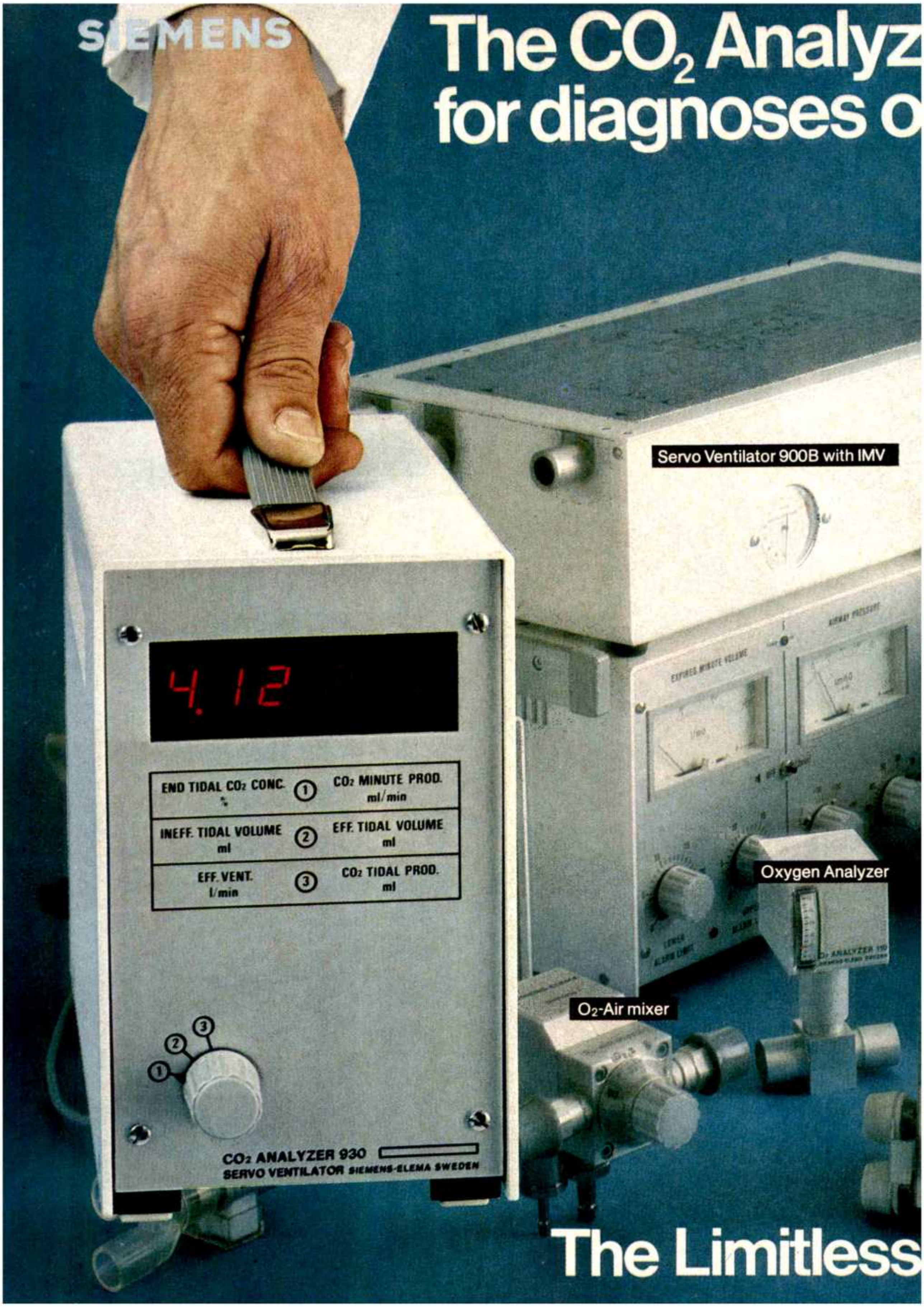
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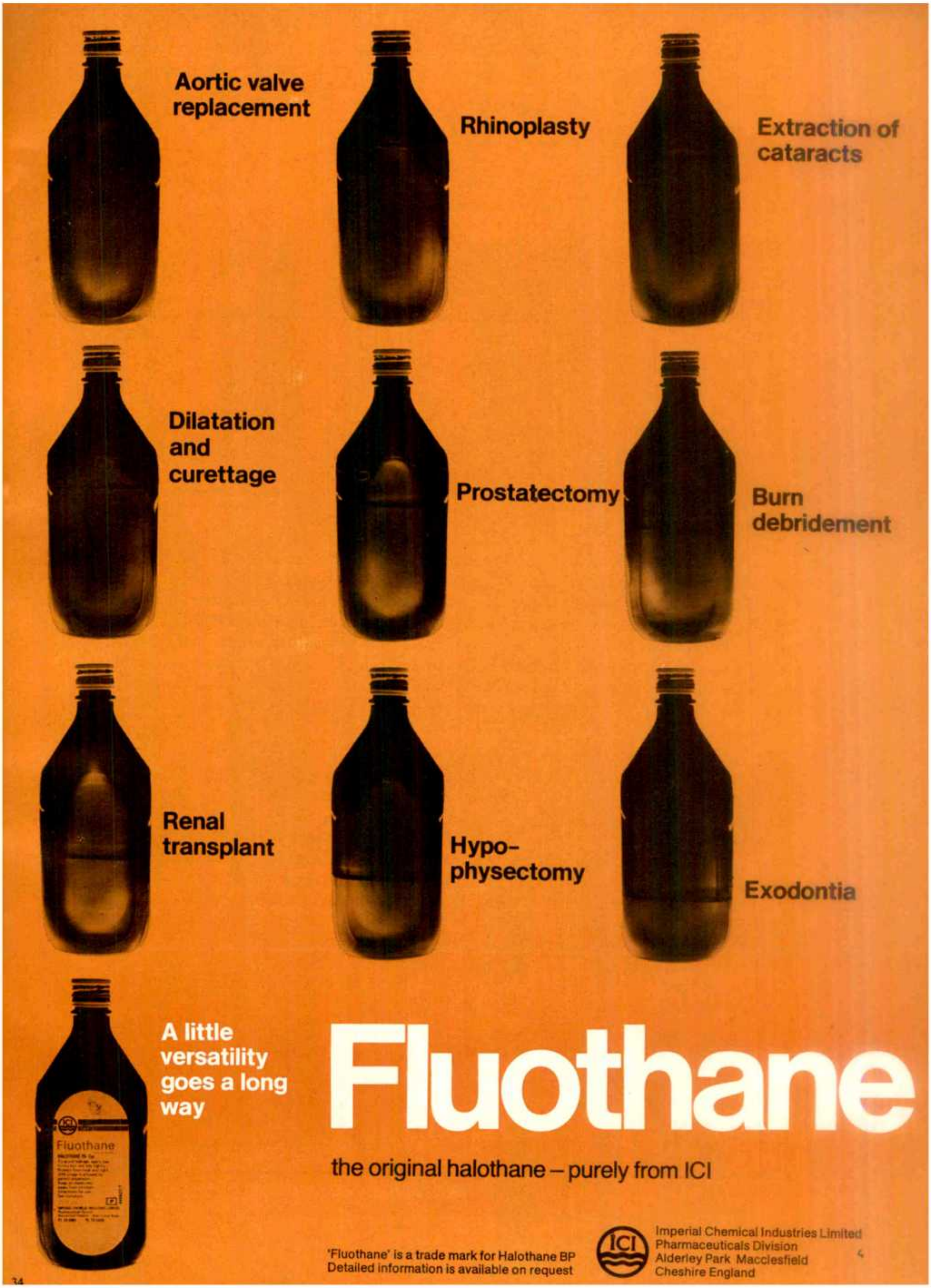

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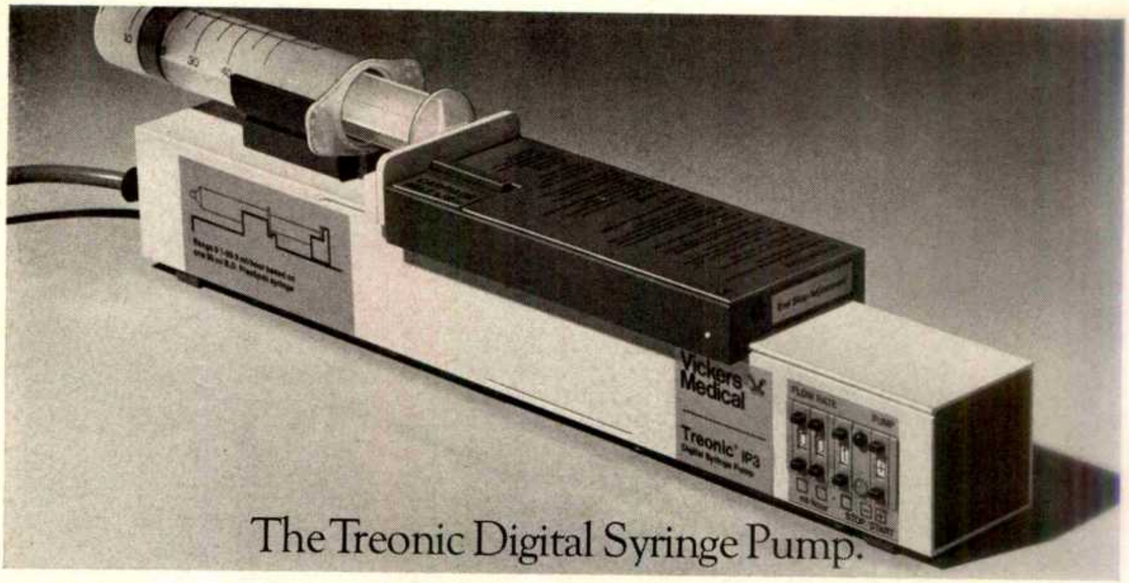

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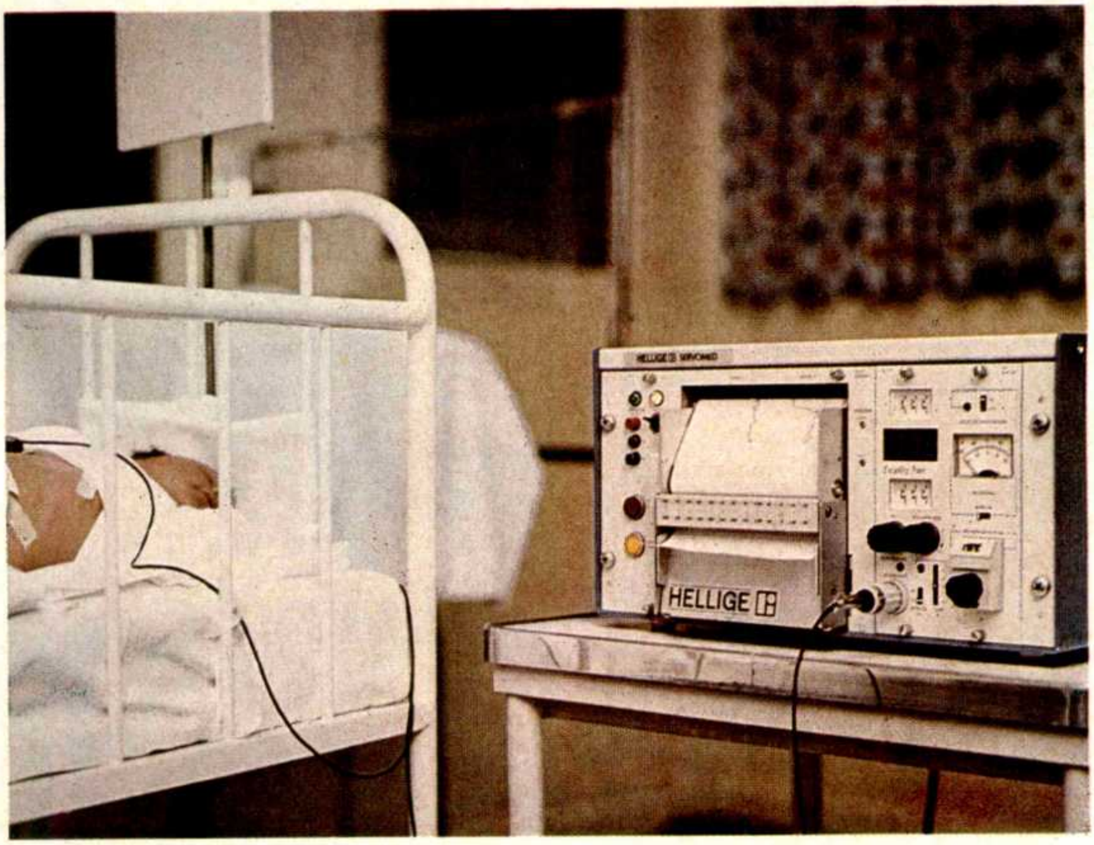

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EDITORIAL

HUMIDIFICATION IN ANAESTHESIA

Nine years ago, a leading article in this journal (Editorial, 1970) drew attention to a paucity of information on the humidification requirements for patients undergoing prolonged anaesthesia. Despite continuing research in the intervening period, we are still not in a position to be any more dogmatic.

The possible beneficial effects of humidification are twofold: prevention of lung damage and conservation of heat. It is clear that drying of the respiratory tract with subsequent epithelial desquamation will be minimized and the secretions moved more easily by humidification of the inspired gas. However, humidification is not without potential disadvantages, including bronchoconstriction, energy losses at the gas–liquid interface and swelling of secretions producing an increase in airways resistance. Water intoxication may occur with ultrasonic aerosol nebulizers, although modern apparatus may be operated at less than maximum output.

Traditionally, humidification has been used during general anaesthesia to prevent both thermal and water loss from infants and small children. However, even when high-flow non-rebreathing systems are used, water loss may be countered easily by oral or i.v. administration of fluid and, in any case, is tolerated easily by the well-hydrated infant (Graff, 1975). Heat loss may be prevented by the use of modern efficient systems of conduction or radiation heating of the infant.

Heat loss in adults has been reduced by the use of heated humidity or a soda-lime absorber, a heat and moisture exchanger (HME), or both, in the anaesthetic circuit, particularly in the U.S.A. Although theoretical benefit may be expected from humidification in prolonged operations with a wide surgical exposure, for example during major vascular surgery, it is difficult to define the duration or extent of surgery which warrants humidification either to aid in the control of thermal loss (Lunn, Mapleson and Hillard, 1971) or to promote ciliary activity and mucous flow, and thereby protect the underlying mucosa during ventilation.

In clinical practice, there is no clear criterion of the effectiveness or otherwise of humidification during anaesthesia, if the misuse of aerosol nebulization is discounted. It was suggested that the absence of humidification caused an increase in chest complications after operation (Stevens and Kennedy, 1968) but this has not been confirmed (Knudsen, Lomholt and Wisborg, 1973). It may be that potential benefits of humidification during anaesthesia are too small to be detectable by relatively insensitive tests of pulmonary dysfunction.

Recently, there have been studies of penetration by aerosols as a more efficient means of softening and loosening mucus plugs. (Such studies are clearly more appropriate to the intensive therapy unit and may not be useful in elucidating the role of humidification in anaesthesia.) Early theory, based on experimental evidence concerning the behaviour of dusts, suggested that small particles (1 μm) would penetrate as far as the alveoli and, if small enough (0.5 μm or less), possibly return to more proximal airways in the carrier gas stream. However, the fate of dusts may not be the same as that of water. Water droplets exist in equilibrium with water vapour, some of which is derived from vaporization from the reservoir of water (especially when it is heated) and the remainder from evaporation of the droplets themselves. Nonetheless, it is possible to calculate from the size of the droplets and the size of the airways the likely extent of penetration of the respiratory tract by aerosols. Despite such theoretical calculations showing that penetration should be excellent, doubts about the clinical effectiveness of aerosols have led to studies of particle penetration at various levels in the bronchial tree using radioactive tracer techniques.

With such methods, Avery, Galina and Nachman (1967) could find no persistence of water in the droplet phase beyond the third generation of bronchi, and they questioned the rationale of mist therapy when the patient had disease affecting the smaller airways predominantly. It was shown that the mist from ultrasonic nebulizers penetrated only to a very limited degree if the mist was directed through the pharynx and larynx rather than through an endotracheal tube or tracheostomy. Because of fears of over-hydration on the one hand, and apparent clinical failure on the other, mist therapy has become less popular in recent times except in conditions where tenacious secretions are a predominant feature, as in mucoviscidosis.

Heated water vapour remains the most popular form of humidification of the respiratory tract. The average heated water bath humidifier is capable of an output (relatively independent of ventilatory flow rates) of 60–85% relative humidity at body temperature, corresponding to water contents of 26 and 37 g m^{-3} respectively. The maximum output may be boosted to 90% or even 100% by attention to the design of the vaporization chamber and its outflow. Clearly, the aim has been to mimic the condition of saturation at body temperature (44 g m^{-3}) which is assumed to obtain normally in the human respiratory tract (Déry, 1973; Shanks and Sara, 1973). However, doubts have been cast on the wisdom of applying such high humidity at or around body temperature. From examination of the canine airway using electronmicroscopy, Tsuda and his co-workers (1977) have concluded that the least epithelial desquamation and damage was associated with the application of 100% relative humidity at only 25 °C (corresponding to a water content of about 24 g m^{-3}) whilst pulmonary dysfunction occurred at temperatures in excess of 30 °C (Noguchi, Takumi and Aochi, 1973). Although it has been shown in intensive therapy that an association between high humidity and pulmonary dysfunction could be a complication of aerosol therapy (Modell et al., 1968), it is postulated that a reduction in arterial P_{O_2} in association with high inspired humidity was a result of water vapour alone (Josenhans, Melville and Ulmer, 1969).

The role of humidification in anaesthesia remains uncertain. Those who advocate its use do so not by virtue of a weight of scientific data, but by the desire to mimic a natural process. Those who choose not to employ humidification question the evidence for its value and point to the hazard of excessive humidification. Clearly this is an area which is important to all anaesthetists and one which warrants further study.

Bernard Hayes

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MEASUREMENT OF THE RELATIVE CONTRIBUTIONS OF RIB CAGE AND ABDOMEN/DIAPHRAGM TO TIDAL BREATHING IN MAN

D. FAITHFULL, J. G. JONES and C. JORDAN

SUMMARY

A simple mathematical model of the chest wall was constructed so that during tidal breathing the relative volume contributions of the rib cage and abdomen/diaphragm could be measured in man, using four mercury-in-rubber strain gauges around the trunk. From the dimensions of the trunk and the change in circumference determined by the four gauges, the separate contributions of rib cage and abdomen/diaphragm could be determined using a purpose-built analog computer. The system was evaluated in 13 laboratory personnel, and in 13 other subjects before and after anaesthesia. There was a linear relationship between tidal volumes computed and measured at the mouth, over the residual volume to (FRC+1 litre) range, with an error of ±8%. The relative contribution of rib cage to tidal breathing showed a large scatter from 5 to 42% with a non-significant tendency to decrease with age.

It has been known for more than a century that rib cage movement is impaired selectively during inhalation anaesthesia (Snow, 1858). These observations were extended by Miller in 1925 and incorporated into the well-known Guedel classification of anaesthesia in 1927. However, there has been little further interest shown by anaesthetists in the significance of this effect. This may be a result of the increasing realization of the complex interaction of the rib cage and diaphragm which deterred investigators from making more detailed studies of the chest wall during anaesthesia. Following the work of Konno and Mead (1967), techniques have been developed which enable further advances to be made in the understanding of chest wall function during anaesthesia. This study describes a technique designed to integrate chest wall movements and partition rib cage and abdomen/diaphragm contributions to tidal breathing so that the effects of inhalation anaesthesia on chest wall function may be examined in man.

METHODS AND RESULTS

The method was devised so that changes in lung volume could be derived from the change in circumference of the rib cage and abdomen, measured with a number of mercury-in-rubber strain gauges around the trunk. In this way the relative movements of rib cage and abdomen/diaphragm could be demonstrated with their respective contributions to any reduction in lung volume which follows induction of anaesthesia. Quantitative measurement over the vital capacity range was not required, hence mathematical complications arising from other dimensional changes at extremes of lung volume (e.g. vertebral column extension or elevation of the edge of the diaphragm) did not need consideration. All subjects were studied in the supine position, thus postural changes could be ignored.

A simple geometrical model of the chest wall was produced (fig. 1). The chest cavity is usually elliptical in cross section, but in this model it was assumed to be circular and in the form of a truncated cone. The error introduced by this assumption is discussed below. The abdominal cavity was also assumed to have a circular cross-section and be conical in shape. The abdominal contents were assumed to be incompressible and respiratory movements of the diaphragm and rib cage were analysed as a change in circumference of each cavity. At large lung volumes (Agostoni et al., 1965) descent of the dome of the diaphragm is accompanied by elevation of its edge and, over this volume range, change in abdominal circumference may no longer accurately reflect diaphragm movement. Breathing at high lung volume was not part of this study, and this was regarded as a small source of error when breathing over the range from maximum expiration up to 60% inspired vital capacity.

D. FAITHFULL,* B.TECH.; J. G. JONES, M.D., M.R.C.P., F.F.A.R.C.S.; C. JORDAN, B.TECH.; Division of Anaesthesia, Clinical Research Centre, Watford Road, Harrow, Middlesex HA1 3UJ.

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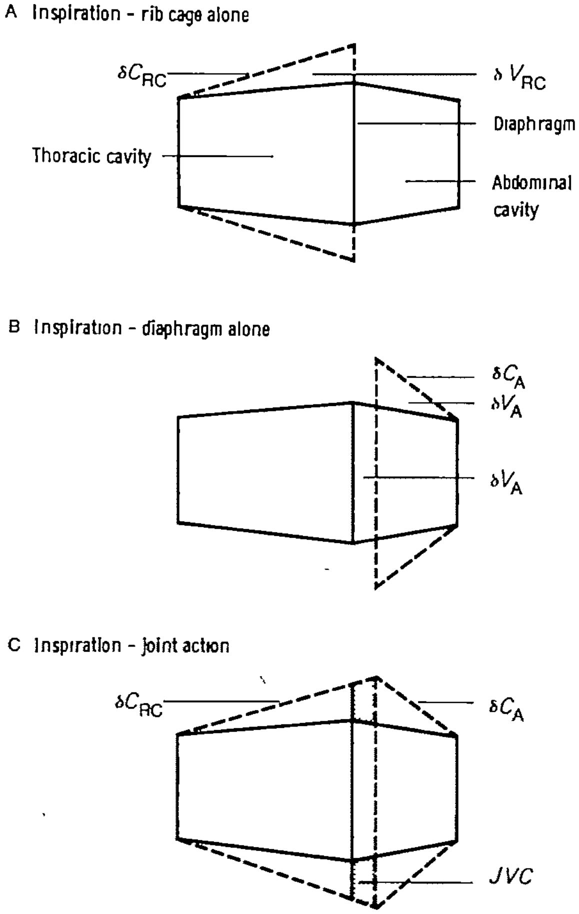

FIG. 1. The mathematical modelling of rib cage and abdomen/diaphragm separately (A and B). When the interaction between rib cage and abdomen/diaphragm is taken into account (C) there is an additional volume (the joint volume contribution). This has to be computed and added to the change in volume of rib cage and abdomen/diaphragm to obtain the total volume. δC_{RC} = change in rib cage circumference; δV_{RC} = corresponding change in rib cage volume; δC_A = change in abdominal circumference; δV_A = corresponding abdomen volume contribution.

The geometrical model

Although the rib cage and diaphragm are not strictly independent mechanically, it is possible to deal separately with the contributions of each to total system volume change.

(1) *Rib cage alone* (*fig.* 1A). If it is imagined that the diaphragm is static and the only contribution to system volume change results from the enlargement of the rib cage, then figure 1 applies. The volume change is the conical annulus denoted by δV_{RC}. This volume is calculated as

$$\delta V_{RC}=H_{RC}/3\pi[\delta C_{RC}^2+\delta C_{RC}(2C_{RC}-C_t/2)]$$

where

C_t is the circumference of the rib cage at the lung apices,

C_{RC} is the mean circumference of the rib cage at its mid-point,

H_{RC} is the total height of the thoracic cavity (from lung apices to diaphragm) and is constant if the diaphragm is assumed to be static.

The difference between C_{RC} and C_t may be significant and hence the equation cannot be simplified. However, if the thoracic cavity is divided into smaller sections and the volume change of each considered separately, a geometrical approximation is possible. The smaller each section is made, the more nearly cylindrical each becomes and the errors in computation resulting from assumptions of uniformity of shape over the section diminish. A compromise has to be made between increased accuracy and the increased complexity resulting from greater numbers of sections.

If each section is considered to be cylindrical, then the volume change resulting from rib cage enlargement is that of a cylindrical annulus. Since the volume of such an annulus is given by

$$V = H/4\pi\ (C_{outer}^2-C_{inner}^2)$$

where

H is the annulus height and C_{outer} and C_{inner} the outer and inner circumferences respectively, then for any section of the rib cage:

$$\delta V_{RC} = H_{RC}/4\pi[(C_{RC}+\delta C_{RC})^2-C_{RC}^2]$$

this reduces to

$$\delta V_{RC} = H_{RC}/4\pi[2\delta C_{RC}\cdot C_{RC}+\delta C_{RC}^2]$$

Typically, δC_{RC} may be <1 cm during tidal breathing and C_{RC} of the order of 100 cm. Hence the factor $2\delta C_{RC}\cdot C_{RC}$ is approximately 100 times larger than δC_{RC}^2, which can therefore be ignored. Thus,

$$\delta V_{RC} = H_{RC}/2\pi\cdot\delta C_{RC}\cdot C_{RC}$$

If the rib cage is divided into two sections, each of circumference C_{RC_1} and C_{RC_2} and height H_{RC_1} and H_{RC_2}, the total rib cage volume change is given by

$$\delta V_{RC} = 1/2\pi[H_{RC_1}.\delta C_{RC_1}.C_{RC_1}+H_{RC_2}.\delta C_{RC_2}.C_{RC_2}]\ \text{(i)}$$

when the sections change in circumference by δC_{RC_1} and δC_{RC_2}.

(2) *Abdomen/diaphragm alone* (*fig.* 1B). For the derivation of (i) it was assumed that the diaphragm was static so that the height of the thoracic cavity, $H_{RC_1}+H_{RC_2}$, remained constant. The contribution from the abdomen/diaphragm can be determined in the following manner.

With the rib cage held static at end-expiration, and the diaphragm free to move, the abdomen volume contribution is approximately equivalent to a cylinder of height equal to the amount of diaphragm lowering, and circumference equal to that of the bottom of the rib cage. This volume is shown as δV_A in figure 1B.

To compute the diaphragm contribution, the extent of diaphragm movement δD from end-expiration must be known. Since the abdominal contents are incompressible, this can be shown to be

$$\delta D = (2\delta C_A.H_A)/(C_A+2\delta C_A)$$

where

H_A = height of abdominal cavity from pelvic basin to position of diaphragm at end-expiration,

C_A = abdominal circumference at end-expiration,

and using an expression similar to that used for the rib cage (equation (i)), the abdomen/diaphragm contribution can be calculated:

$$\delta V_A = \frac{(H_A-\delta D)\cdot\delta C_A.C_A}{2\pi} \qquad \text{(ii)}$$

(3) *Joint volume contribution* (JVC). Figure 1C shows the more realistic situation where, because of the coupling of the diaphragm to the rib cage, diaphragm lowering during inspiration is responsible for rib cage enlargement. The shaded area, termed the Joint Volume Contribution, is unaccounted for in either equation (i) or (ii). This joint volume contribution can be approximated to a cylindrical annulus at the junction of the rib cage and the abdomen so that

$$\mathcal{J}VC = \frac{\delta D.\delta C_{RC_2}.C_{RC_2}}{2\pi}$$

Substituting for δD:

$$\mathcal{J}VC = \frac{1}{\pi}\cdot\frac{\delta C_A.\delta C_{RC_2}.H_A.C_{RC_2}}{C_A\cdot 2\delta C_A} \qquad \text{(iii)}$$

(4) *Total volume change.* The total volume change, the tidal volume, is the sum of the rib cage, abdomen and joint contributions. Hence:

$$V_{\text{total}} = V_{RC}+V_A+\mathcal{J}VC$$

Because both the abdomen/diaphragm and the joint volume contributions result from diaphragm contraction, δV_A and $\mathcal{J}VC$ can be combined to give the actual volume contributed by diaphragm contraction, $\delta V_{A_{\text{actual}}}$. To simplify the computational steps in the analog computer, the expression solved was

$$\delta V_{A_{\text{actual}}} = \frac{H_A\cdot\delta C_A\cdot C_A}{2\pi} \qquad \text{(iv)}$$

This describes the sum of the volumes of equations (ii) and (iii) and assumes that, at the junction of rib cage and abdomen:

$$C_A = C_{RC_2} \quad \text{and} \quad \delta C_A = \delta C_{RC_2}$$

It must be emphasized that this equation is only a good approximation when circumference changes are small.

Analog computer

Equation (iv) was solved using a purpose-built analog computer. The overall scheme is shown in figure 2. Variable inputs to the system are the signals from the four gauge amplifiers. The circumferences at each gauge position were measured and set up on the appropriate multiturn potentiometer (set C_{RC_1}, C_{RC_2}, C_{A_1} and C_{A_2}). The height of the trunk was measured between the suprasternal notch and symphysis pubis. The diaphragm position was estimated by percussion of the upper margin of the liver, enabling partitioning of the trunk height into the appropriate sections (H_{RC_1}, H_{RC_2}, H_A) which were also entered as parameters. Adjustments of the height parameters were made following the method of Konno and Mead (1967) so that, with the glottis closed, moving the abdomen/diaphragm gave equal and opposite movements of the rib cage. In this way H_A and H_{RC_2} could be varied separately, keeping the sum $H_A+H_{RC_2}$ constant until, with glottis closed, rib cage and abdominal volume contributions were equal.

The volume contributions of rib cage and abdomen/diaphragm, the joint volume contribution and the sum of the rib cage and abdomen/diaphragm were displayed separately on a Devices chart recorder.

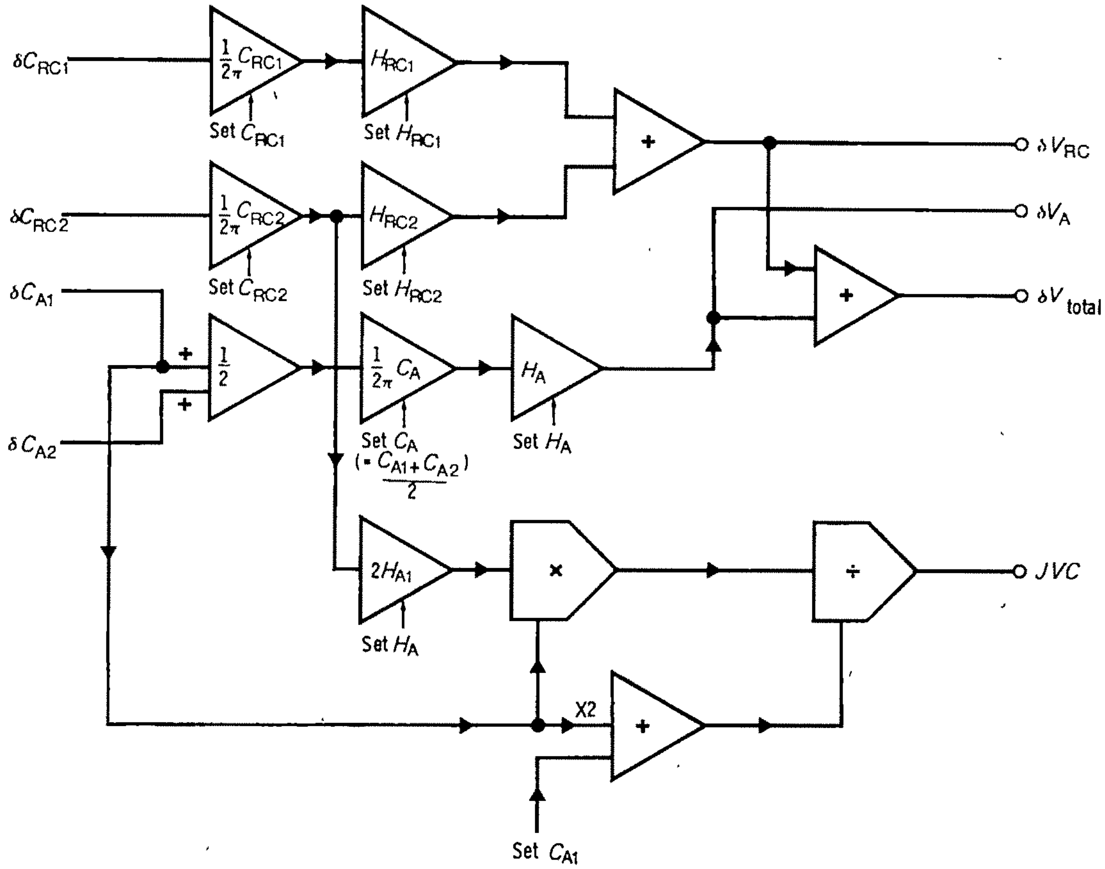

FIG. 2. The general arrangement of the analog computer. The variable inputs are indicated on the left (δC_{RC_1}, δC_{RC_2}, δC_{A_1} and δC_{A_2}). The set values are obtained from measurements of circumferences at the four gauge positions. Set C_{A_1} is the circumference of the upper abdomen, which is used in the computation of the joint volume contribution. The arithmetic operators indicate the function of the operational amplifiers.

Evaluation of the system

Initial work showed that in some subjects non-uniform abdominal shape changes occurred during tidal breathing. This potential source of error was reduced by the application of a second gauge to the abdomen, hence the additional parameters C_{A_1} and C_{A_2}.

Thirteen male laboratory personnel were studied in the supine position while breathing into a bag-in-box system connected to an Ohio electronic spirometer. The tidal volume measured with the spirometer was compared with the computed δV_{total}. Ventilation was increased by adding carbon dioxide to the system and the spirometric and computed tidal volumes were recorded on the Devices recorder. The mean of four consecutive breaths at each of three different tidal volumes was used to prepare a composite plot of computed against measured tidal volume (fig. 3). These data were supplemented by tidal volume measurements in a group of four female and nine male patients with a larger age range than the laboratory personnel. These patients gave informed consent to the non-invasive procedure. The mean (±1 SD) of the dimensions of the trunk for this group of 26 subjects is shown in table I. The patients were studied immediately before and after the induction of anaesthesia with thiopentone and 1% halothane in a nitrous oxide in oxygen mixture. In the patients, tidal volume was determined by electronic integration of flow at the mouth, which was measured using a Fleisch II pneumotachograph and Validyne Pressure transducer. This system was calibrated with the anaesthetic gas mixture using a 1-litre Hamilton syringe. The results show that the reduced tidal volume during anaesthesia is accurately computed from the movements of the surface of the body (fig. 3). In this group of 26 subjects, 94% of the computed values were within ±8% of the

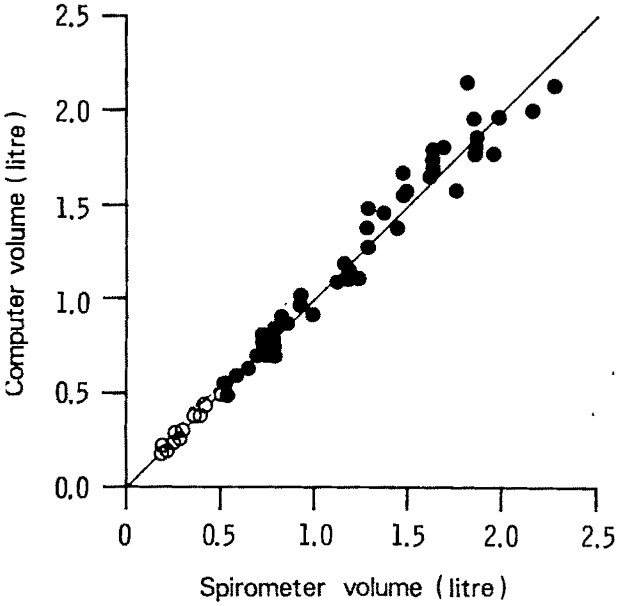

FIG. 3. Comparison of measured tidal volume and computed tidal volume in 26 subjects. Closed circles represent data from conscious subjects and open circles those from anaesthetized subjects. Each closed circle represents the mean of four consecutive breaths. An increase in tidal volume was obtained by increasing alveolar carbon dioxide. Sources of system error are shown in table II.

TABLE I. *The mean* (±1 SD) *of rib cage, abdominal circumference and height and the change in circumference (cm) during tidal and vital capacity breathing* (n = 26)

	Rib cage	Abdomen
Height (cm)	26.5±4.5	29.2±6.2
Circumference (cm)	92.6±6.9	82.4±8.8
Δ Circumference (tidal) (cm)	0.41±0.33	1.39±0.4
Δ Circumference (VC) (cm)	3.31±1.74	3.78±1.38

directly measured tidal volume. The sources of system errors are shown in table II.

The 13 laboratory personnel were also studied while breathing predominantly with rib cage or abdomen. Ten of these subjects were able to achieve 85% of tidal ventilation with either rib cage or abdomen. In those subjects breathing predominantly with the abdomen, there was a close fit between spirometric measurements and computed volumes, the measurement error being less than ±4%. With predominant rib cage breathing the error increased, with a tendency to overestimate the tidal volume by 15% in two subjects. The mean computed tidal volume for rib cage breathing was 9% greater than the spirometer volume with a range of 2–15%. The data from the laboratory personnel were also displayed as an X–Y plot of spirometer volume against computed volume while the subjects breathed slowly from functional residual capacity (FRC) to residual volume (RV) and then to total lung capacity. Two of 13 subjects showed non-linearity near RV, beginning at about 100 ml above RV, and these subjects showed gross deformity of the abdominal wall shape at this stage of the manoeuvre. Five subjects showed non-linearity beginning at about 60% vital capacity, the computed volume underestimating the real change in lung volume. The remaining subjects showed a linear relationship similar to that shown in figure 4.

TABLE II. *Effect of system errors on computed tidal volume*

Variable	Error in computed volume
Measurement of circumference	±1%
Measurement of height	±5%
Cross sectional shape of rib cage	+6%
Gauge non-linearity	±4%
Computational errors	±9%

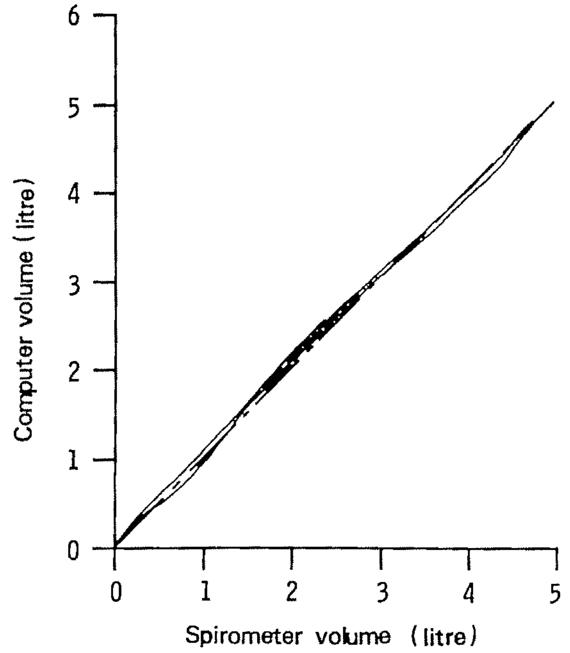

FIG. 4. Vital capacity manoeuvre in one subject to show linear computation of volume. Similar results were found in four other subjects although the design specification of the system did not require measurement of large changes in lung volume.

X–Y plots were made of rib cage *v.* abdomen during tidal breathing in all 26 subjects. This showed a wide variability of rib cage contribution ranging from 5 to 42% of tidal volume in these non-anaesthetized subjects (fig. 5). This seemed to be age-related, in that no subject over 50 years of age had a rib cage contribution exceeding 20% of tidal volume. However, this relationship was not statistically significant. There was no consistent difference in the rib cage contribution between male and female patients, but the number of female patients was small.

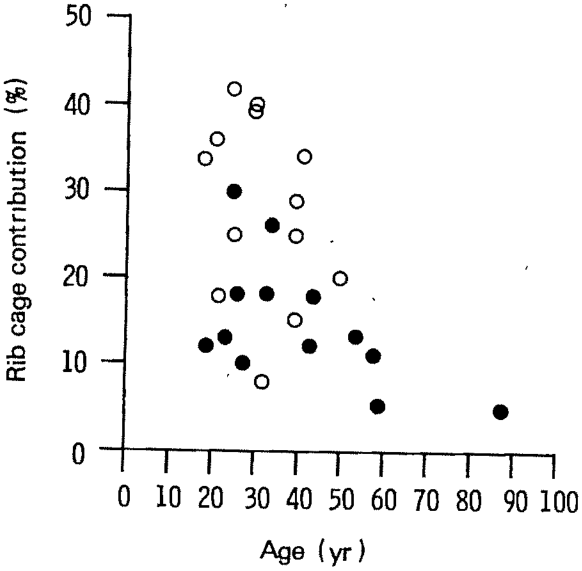

FIG. 5. Fractional contribution of rib cage to tidal volume against age for the 26 subjects studied. Open circles: laboratory personnel; closed circles: patients studied before anaesthesia.

To see if this large variability could be explained by differences in breathing rate, a study was carried out in three subjects, on the effect of varying breathing frequency on the rib cage contribution to tidal volume. Each subject breathed first at his normal rate then in time to a metronome. Two of the three subjects showed a small increase in rib cage contribution with increasing frequency while the third showed a slight decrease (fig. 6). Variations in frequency over the normal physiological range produced only trivial changes in rib cage contribution. One of the subjects breathed through a constricted tube equivalent to a resistance of 1 kPa litre^{-1} s. This subject showed quite a large increase in rib cage contribution until the respiratory rate reached 50 b.p.m., when a large phase lag of about 90° appeared between the two signals (fig. 6).

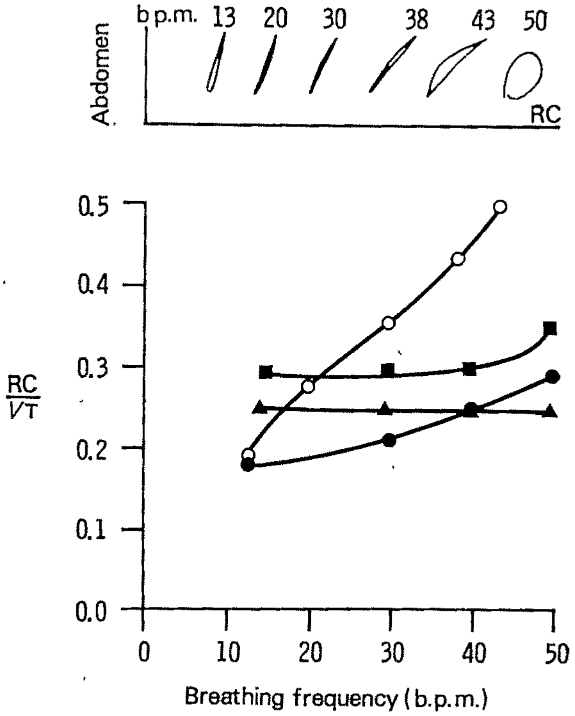

FIG. 6. Effect of breathing frequency on fractional rib cage contribution in three subjects, A (●), B(■) and C (▲). Subject A was also studied while breathing through a constricted tube of resistance 1 kPa litre^{-1} s (○). The data from this latter study are represented as *X–Y* plots of rib cage (RC) against abdomen in the top part of the figure. The respiratory rate (b.p.m.) is indicated. Note the large phase lag when breathing at 50 b.p.m.

DISCUSSION

Detailed studies of the relative contributions of the rib cage and abdomen/diaphragm have only been made in the past decade, but these have been confined to studies of conscious subjects. A notable advance was made by Konno and Mead (1967) who showed that, in conscious man, the relative volume contribution to breathing of the rib cage and abdomen could be measured from changes in the anterior-posterior diameters at only two points, using magnetometers, one on the rib cage and the other on the abdomen. A fundamental assumption was that, although the chest wall was quite irregular in shape, the movement of one part of the rib cage bore a constant relationship to the movement of any other part and, similarly, the movement of one part of the abdomen was in constant proportion to that of any other part of the abdomen. When the glottis closed, the subjects changed the shape of the chest and abdomen, displacing volume from one compartment to another. In this system (with one degree of freedom) the gains of the abdominal and rib cage signals could be made equal so that, with the glottis open, the sum of rib cage and abdominal signal could be made equal to tidal volume. As Konno and Mead (1967) and later Mead (1974) have pointed out, this method relies on the chest wall changing its shape uniformly, and in conscious subjects this is probably the case in most circumstances. The method is invalid if the shape of the chest wall changes in a non-uniform fashion, which occurs with changes in pleural pressure beyond the limits of ordinary breathing, such as during muscular efforts against a closed airway and during loaded breathing. These pleural pressure changes affect adversely the stability of the chest wall shape which is normally maintained by a highly integrated reflex control system (Sears, 1973). Impairment of this uniform movement of the chest wall is likely when the reflexes stabilizing the position of the rib cage are attenuated during anaesthesia, although errors induced by non-uniform movements of the rib cage may not be recognized because of its small contribution to tidal breathing. However, if the phase relationships between rib cage and abdomen are to be studied, then considerable errors may arise if one part of the rib cage such as the sternum is being displaced inwards while the rib margins in the mid-axillary line are displaced outwards. This study describes a technique designed to overcome this objection by integrating chest wall movement from measurements of changes in circumference of the trunk at four sections in awake and anaesthetized man. However, using this technique two potential sources of error remain.

The first of these is the assumption that the trunk is of circular cross-section. Our model also assumed a cylindrical rather than a conical shape for the chest wall. With typical parameter values found in our subjects, the assumption of a cylindrical rather than conical shape can be shown to produce an underestimation of tidal volume of about 0.6%. Agostoni and colleagues (1965) made lateral and anterior-posterior measurements of the trunk which showed that an elliptical cross section is a better approximation. The average ratio of these measurements in both sitting and supine positions was found to be 1.42 : 1 (range 1.18–1.49). It is possible to calculate that, in assuming a circular cross-section, the error in computed volume for this average ratio is an overestimation of about 6%. This assumes that equal relative changes occur in both the major and minor axes of the elliptical cross section.

The second potential source of error arises from the basic geometrical assumptions made about the diaphragm. We were not sure what effects non-planar movements of the diaphragm would have on the computation of the abdominal contribution. In theory, since the abdominal contents are incompressible, whatever contribution the diaphragm makes to tidal volume should be accurately reflected in the change in the circumference of the abdomen. It is the effective diaphragm position, therefore, that is important and this is represented as the plane in our model. The implication is that this effective position can be determined accurately. This is obviously difficult and may well have contributed to the computational errors. In order to determine the effect of errors in estimation of diaphragm position we have computed the change in rib cage, abdominal and total volume (tidal volume) (fig. 7) using the mean values for rib cage and abdominal circumference and height shown in table I. This showed that the rib cage contribution expressed as a percentage of tidal volume was in error by 0.6% per cm error in diaphragm position and tidal volume was in error by 1.7% per cm error. These errors, although small, are minimized by using the Konno and Mead (1967) manoeuvre with glottis closed to adjust the relative heights of the abdomen and rib cage when it protrudes. The error with predominant rib cage

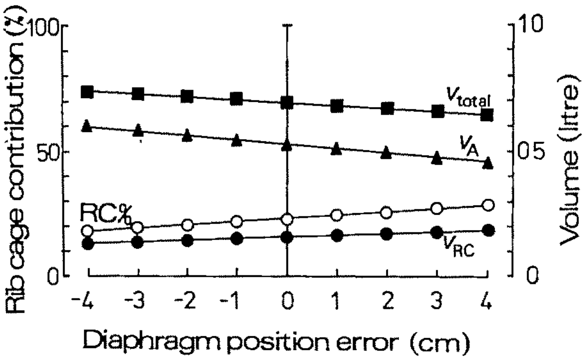

FIG. 7. Computed error in fractional rib cage contribution to tidal volume and in change in rib cage, abdominal and tidal volume when the diaphragm position is estimated incorrectly. Data used to calculate these errors are given in table I. The total height of the rib cage and abdomen is kept constant and the diaphragm position is altered ±4 cm.

breathing tended to increase and produced a consistent over-estimate of the directly measured tidal volume. It was felt that, because the range of movement of the rib cage in these manoeuvres was different from that expected during anaesthesia, this effect was acceptable for the purpose of the study.

The relative contribution of the rib cage to tidal breathing varied widely in the subjects in this study. It has been reported previously that in the supine position the rib cage contribution is about 30% of tidal volume, whereas the mean value for our subjects was 22% (range 5–42%). That this was not a result of differences in breathing frequency was suggested by a study of the effect of breathing rate on rib cage contribution in these subjects. This showed only minute changes over the physiological range in patients who had normal airway resistance. It was also noted that the laboratory staff group had a higher mean rib cage contribution (28%) than the patients (15%) and although the patients were older than the laboratory group, there was no statistically significant relationship with age.

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MESURE DES CONTRIBUTIONS RELATIVES DE LA CAGE THORACIQUE ET DE L'ABDOMEN/DIAPHRAGME A LA RESPIRATION DE CHEYNE-STOKES CHEZ L'HOMME

RESUME

Un modèle mathématique simple de la paroi de la poitrine a été construit afin que l'on puisse mesurer, chez l'homme, le volume relatif des contributions de la cage thoracique et de l'abdomen/diaphragme pendant la respiration de Cheynes-Stokes, et ce à l'aide de quatre extensiomètres à mercure dans du caoutchouc placés autour du tronc. A partir des dimensions du tronc et des variations de la circonférence déterminées par les quatres extensiomètres, on a pu déterminer les contributions individuelles de la cage thoracique et de l'abdomen/diaphragme grâce à un ordinateur analogique construit dans ce but. Le système a été évalué sur 13 membres du personnel du laboratoire et sur 13 autres avant et après anesthésie. Il y a eu une relation linéaire entre les quantités d'air expiré à chaque respiration, calculées et mesurées à la bouche, par rapport au volume résiduel (FRC÷1 litre), avec un écart de ±8%. La contribution relative de la cage thoracique par rapport à la respiration de Cheyne-Stokes a montré une grande dispersion allant de 5 à 42% ainsi qu'une tendance non significative à décroître avec l'âge.

MESSUNG DER RELATIVEN BEITRÄGE VON BRUSTKORB UND UNTERLEIB/ZWERCHFELL ZUM MENSCHLICHEN ATMUNGSVORGANG

ZUSAMMENFASSUNG

Ein einfaches mathematisches Modell der Brustwand wurde konstruiert, um bei natürlicher Atmung die relativen Volumsbeiträge des Brustkorbs und des Unterleibs/Zwerchfells beim Menschen mittels vier um den Rumpf gewickelten Quecksilber–Gummimessgeräten messen zu konnen. Aus den Abmessungen des Rumpfes und den Umfangsveränderungen, gemessen durch die vier Geräte, konnten die jeweiligen Beiträge von Brustkorb und Unterleib/Zwerchfell mittels eines speziell konstruierten Analogkomputers bestimmt werden. Dieses System wurde an 13 Laboratoriumsangestellten ebenso erprobt wie an 13 anderen Personen vor und nach Narkose. Es bestand ein lineares Verhältnis zwischen über dem Mund gemessenen und berechnetem Atemvolumen und dem Restvolumenbereich (FRC+1 Liter) mit einem Fehlerbereich von ±8%. Der relative Beitrag des Brustkorbes zur Atmung zeigte eine starke Streuung von 5 bis 42%, mit einer unwesentlichen Tendenz des Absinkens im Alter.

MEDICION DE LAS CONTRIBUCIONES RELATIVAS DEL COSTILLAJE Y EL ABDOMEN/DIAFRAGMA A LA RESPIRACION CORRIENTE EN EL HOMBRE

SUMARIO

Se construyó un modelo matemático sencillo de la pared del tórax con el fin de poder medir durante la respiración corriente en el hombre las contribuciones relativas de volúmen del costillaje y el abdomen/diafragma, utilizando cuatro deformímetros de "mercurio en caucho", colocados alrededor del tronco. De las dimensiones del tronco y el cambio en su circunferencia determinado por los cuatro deformímetros, pudieron determinarse las contribuciones separadas del costillaje y el abdomen/diafragma, empleando un computador analógico de construcción especial. El sistema fue evaluado con 13 miembros del personal del laboratorio y en 13 sujetos más antes y después de anestesia. Hubo una relación lineal entre los volúmenes de respiración computados y medidos en la boca y el volúmen residual (FRC +1 litro), con un error de ±8%. La contribución relativa del costillaje a la respiración corriente indicó una mayor variación, entre 5 y 42%, con una tendencia no significativa a disminuir a medida que avanza la edad.

Br. J. Anaesth. (1979), **51**, 399

RIB CAGE MOVEMENT DURING HALOTHANE ANAESTHESIA IN MAN

J. G. JONES, D. FAITHFULL, C. JORDAN AND B. MINTY

SUMMARY

Chest wall movement, partitioned into rib cage and abdomen/diaphragm contributions, was measured using four mercury-in-rubber strain gauges and an analog computer. The relative volume contribution of the rib cage and the abdomen/diaphragm to tidal volume was measured in 13 subjects before and during anaesthesia with thiopentone and halothane. In awake subjects, movement of the abdomen/diaphragm contributed more than 70% of the tidal volume, the smaller rib cage contribution ranged from 5 to 30%. Manual ventilation during induction of anaesthesia showed that the rib cage was less compliant than the abdomen/diaphragm, but when suxamethonium was given there was a disproportionate increase in rib cage compliance. In nine out of 12 subjects, halothane anaesthesia resulted in a large decrease in the fractional contribution of the rib cage. In two of these subjects there was paradoxical breathing, the rib cage and the abdomen/diaphragm movement being 180° out of phase. This effect was produced easily in three other subjects by inserting a resistance (1 kPa $litre^{-1}$ s) into the anaesthetic circuit. The technique also produced information about changes in volume of the trunk induced by anaesthesia. Eleven subjects showed an increase in end-expiratory abdominal volume (mean increase 120 ml) during halothane anaesthesia while there was a mean reduction in end-expiratory rib cage volume of 29 ml. We concluded that halothane depressed both phasic and tonic postural reflex activity, which affected predominantly the rib cage musculature. This reduced the amplitude of phasic rib cage movement, impaired stability of the rib cage and predisposed to paradoxical ventilation. The results also suggested that the reduction in lung volume during anaesthesia may result from a loss of postural control of the chest wall and a central shift of blood volume.

Since the pioneering work of Snow in 1858 and of Miller (1925) and Burstein (1942), it has been known that intercostal muscle paralysis accompanies inhalation anaesthesia. Despite recent advances in the understanding of rib cage and abdomen/diaphragm function, described in the important papers of Mead (1974) and Goldman (1974), and with the exception of the recent study of Tusiewicz, Bryan and Froese (1977), there has been a paucity of new information on the effect of inhalation anaesthetics on chest wall function in man.

The chest wall is subdivided into the rib cage and abdomen/diaphragm, which have both supportive and ventilatory functions. These two functions are closely integrated by the central nervous system and their efficacy depends upon two types of motor neuron input, tonic and phasic. The importance of the tonic, non-ventilatory input is less widely appreciated than the phasic input, but it is this type of motor activity which plays a fundamental role in stabilizing the shape of the rib cage so that the function of the diaphragm is optimized (DaSilva et al., 1977). This study was designed to measure the relative volume contributions of the rib cage and abdomen/diaphragm to tidal breathing and to demonstrate that the selective effect of halothane on rib cage movement had important consequences on rib cage stability, the loss of which was an important factor explaining the decrease in lung volume which follows induction of anaesthesia.

METHODS

Movement of the chest wall was measured using four mercury-in-rubber strain gauges, two around the rib cage and two around the abdomen. From measurements of the circumference of the trunk at these four locations, the height of each section and the change in circumference, it was possible to compute the relative volume contributions to tidal breathing of the rib cage and abdomen/diaphragm using an analog computer method described previously (Faithfull, Jones and Jordan, 1979). Measurements of tidal breathing at the mouth were made

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using a heated Fleisch II pneumotachograph connected to either a mouthpiece or an endotracheal tube. The pressure decrease across the pneumotachograph was measured with a Validyne transducer, Model MP 45, pressure range ±0.25 kPa (Northridge, California). Data from the analog computer included signals proportional to the tidal volume contribution of rib cage movement, abdominal wall movement and sum of rib cage and abdomen. These signals, together with flow from the pneumotachograph, were recorded using a modified Akai audio tape recorder, the input and output signals being connected via an eight-channel multiplexer unit. Data were replayed off-line onto a Devices chart recorder, tidal volume at the mouth being obtained by electronic integration of the tape-recorded flow signal.

Procedure

Thirteen patients (mean age 40.4 yr) undergoing routine surgery gave informed consent for the study. Pre-anaesthetic medication comprised atropine alone. All patients were studied in the supine position. Gauges were applied to the trunk and baseline measurements of circumference and trunk height were set up on the potentiometers of the analog computer as described previously (Faithfull, Jones and Jordan, 1979). The patients breathed through a pneumotachograph for control measurements of tidal volume, and for partitioning tidal breathing into the rib cage and the abdomen/diaphragm contributions.

Anaesthesia comprised a standard technique with thiopentone, suxamethonium, nitrous oxide, oxygen and halothane. Measurements of chest wall movements were made continuously and end-tidal halothane concentrations were measured using a Hook and Tucker ultraviolet absorption meter modified to give a 90% rise time of 100 ms to a square-wave input of halothane. The inspired concentration of halothane was adjusted to yield end-tidal concentrations of 0.5, 1.0 and 2.0%. The fractional contribution of the rib cage to tidal breathing at each alveolar halothane concentration was obtained from X–Y plots of rib cage against the abdomen/diaphragm (AD) contribution obtained at different stages of the anaesthetic procedure.

RESULTS

Rib cage and abdomen/diaphragm movement before and immediately after induction

The mean rib cage contribution to tidal breathing before induction was 14.6% ($n = 13$). Following induction of anaesthesia, rib cage contribution was measured during manual inflation of the lungs. In nine patients measurements were made after the administration of thiopentone alone. In five of these patients measurements were repeated after the administration of suxamethonium. In the remaining four patients measurements were made only after the combined administration of thiopentone and suxamethonium. Changes in rib cage contribution are shown in figure 1. The rib cage contribution to tidal volume increased with manual inflation during thiopentone anaesthesia and increased further following neuromuscular blockade with suxamethonium (table I).

These changes may also be expressed as relative compliance (RC/AD) during manual inflation. This ratio increased after suxamethonium (fig. 2). The

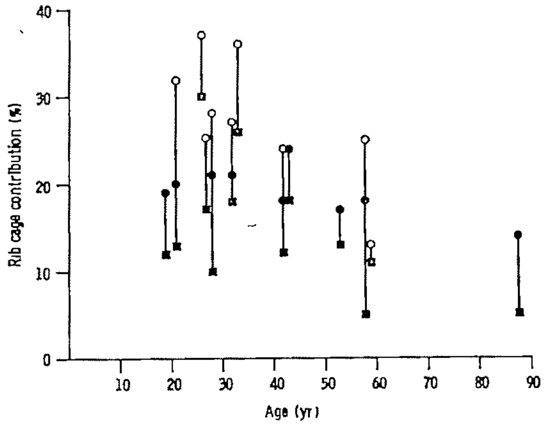

FIG. 1. Fractional volume contribution of the rib cage to tidal volume in 13 patients before and after induction of anaesthesia. All data obtained following induction of anaesthesia were during manual inflation of the lungs. ■ = awake; ● = anaesthetized; ○ = anaesthetized and paralysed.

TABLE I. *Mean (±1 SEM) differences in rib cage contribution, shown in figure 1, on transition from spontaneous ventilation awake to manual ventilation anaesthetized with thiopentone (column 1), thiopentone followed by suxamethonium (column 2) and from awake to anaesthesia with thiopentone and suxamethonium given in rapid succession (column 3)*

	Awake to anaesthetized	Anaesthetized to anaesthetized + paralysed	Awake to anaesthetized + paralysed
n	9	5	9
Mean	+7.3%	+7.6%	+11.7%
SEM	1.07	1.12	2.05
P	<0.001	<0.001	<0.005

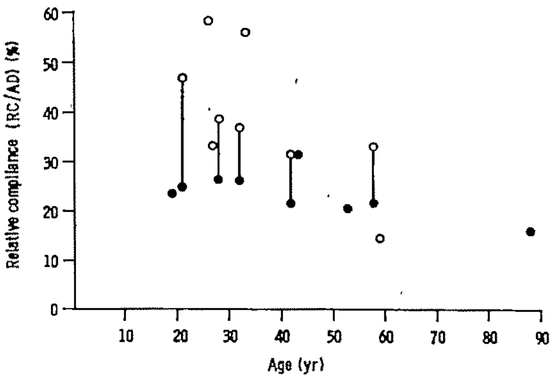

FIG. 2. Relative rib cage compliance derived from the data in figure 1 during manual inflation. ● = anaesthetized; ○ = anaesthetized and paralysed.

elimination of suxamethonium was accompanied by a decrease in compliance of the rib cage and thus returned to the values obtained previously with thiopentone alone. Manual ventilation was usually accompanied by an increase in lung volume which was seen as a shift in baseline of the rib cage and abdominal traces. If the lungs were inflated without permitting the pressure in the airway to decrease to atmospheric, a characteristic series of changes were observed. After an initial increase in rib cage and abdominal girth, the rib cage girth decreased to its original value and the abdomen continued to increase in size. Within a few seconds the circulation had adjusted so that both rib cage and abdomen changed in circumference together.

Phase relationships at onset of and recovery from anaesthesia

Nearly all subjects showed a narrow loop and thus a close-phase relationship between rib cage and abdominal movement when awake and when anaesthetized. An example of this pattern is shown in one subject in figure 3. A few subjects showed larger phase differences with quite wide loops while awake, but during anaesthesia the loop area in every subject always became much less (fig. 4). Immediately following administration of thiopentone there was either a small reduction in rib cage contribution, the rib cage–abdomen loop resembling that seen with low concentrations of halothane, or there was a transient large phase difference with wide loops progressing rapidly to apnoea. Onset of spontaneous respiration with halothane showed a reduction in the area of the rib cage–abdomen loop, a diminished rib cage contribution and in most instances the inspiratory and expiratory parts of the loop were superimposed. On recovery from anaesthesia (fig. 3) there was usually gross phase lag between the two signals which often lasted as long as 1 min before reappearance of the phase relationship that characterized the pre-anaesthetic control pattern.

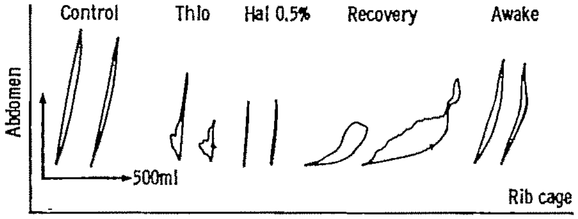

FIG. 3. X–Y plots of volume contributions of rib cage and abdomen/diaphragm. The gain for each signal was the same. This patient showed a close phase relationship both before anaesthesia (control) and with 0.5% alveolar halothane. There was a much larger asynchrony of rib cage and abdomen during induction of anaesthesia and particularly during recovery from anaesthesia. When awake at the end of the anaesthetic the loops were similar to control.

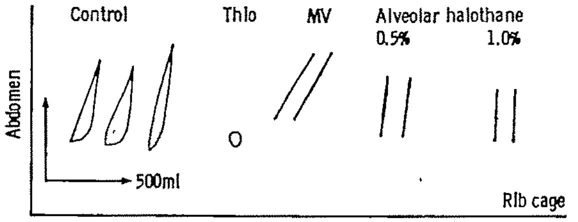

FIG. 4. Loops of larger areas were seen in control breaths of some patients. An example of this pattern is shown in this patient in whom, on induction with thiopentone (Thio), the rib cage and abdomen/diaphragm became 90° out of phase just before ventilation ceased. Also shown are the relative contributions of rib cage and abdomen during manual ventilation (MV) and during halothane anaesthesia. Note that the change in slope of the loop with halothane anaesthesia indicates a reduction in rib cage activity.

Effect of "steady-state" halothane anaesthesia on ches wall movement

In nine of 12 subjects there was a reduction in rib cage contribution with halothane anaesthesia. This was related to the alveolar halothane concentration in such a way that 1% alveolar halothane produced a mean reduction of 50% in rib cage contribution compared with awake controls (fig. 5). Two per cent alveolar halothane resulted in a further reduction in rib cage contribution. In two subjects the rib cage and abdomen became opposite in phase, so that there was a negative contribution of the rib cage

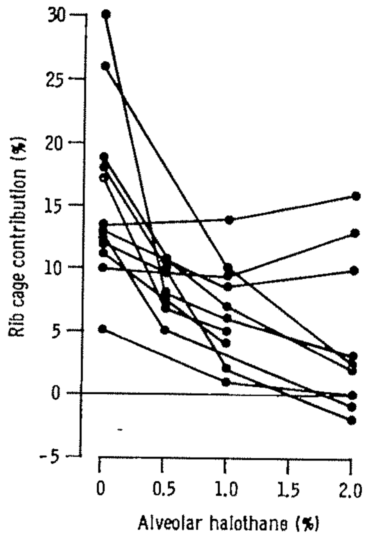

FIG. 5. With increasing alveolar halothane concentration the fractional contribution of the rib cage decreased in all but three subjects. In two subjects with alveolar halothane of 2.0% there was paradoxical ventilation.

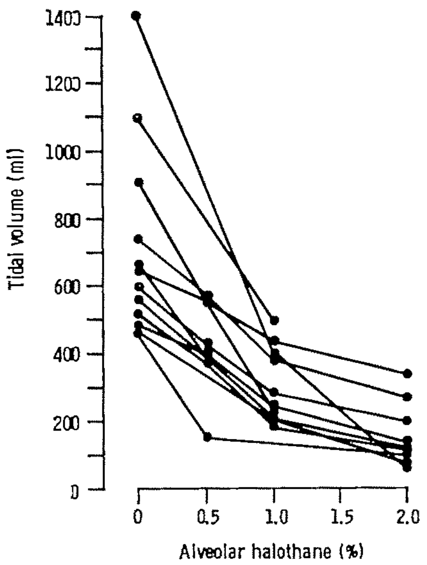

FIG. 6. The reduction in tidal volume in all subjects with increasing halothane concentration. In every case the reduction in tidal volume was accompanied by an increase in respiratory frequency.

and it was pulled inwards by the contracting diaphragm.

There was also a reduction in tidal volume (fig. 6) and an increase in breathing frequency in all subjects. The three subjects showing an increase in rib cage contribution had particularly small tidal volumes (< 100 ml) and larger breathing frequencies (> 60 b.p.m.); one of these subjects had the largest pre-anaesthetic tidal volume (1400 ml) and the smallest tidal volume (85 ml) with 2% alveolar halothane.

Effect of resistive loading

In three subjects a resistive load of 1 kPa litre^{-1} s was added to the breathing circuit during the control period and then during anaesthesia. No change in tidal volume or in the relative contribution of the rib cage was noted during the control period. During anaesthesia there was an immediate decrease in tidal volume and the rib cage contribution became opposite in phase to movement of the abdomen/diaphragm. As carbon dioxide drive to respiration increased there was an increase in abdominal excursion and a further indrawing of the rib cage during inspiration.

In these subjects the mean rib cage contribution before the load was 2% of the tidal volume. Immediately after addition of the load there was an immediate decrease in tidal volume with a negative rib cage contribution of 3% of the tidal volume which, with increasing carbon dioxide drive showed further paradoxical movement, negative rib cage contribution increasing to a mean of 10%. This implied an emptying of alveoli in the upper part of the chest during diaphragmatic inspiration, thus adding alveolar gas to the inspired deadspace.

Effect of anaesthesia on the end-expiratory chest wall position

The end-expiratory level of the rib cage and abdomen/diaphragm signals was found by a line of best fit drawn through a 10-min control period before anaesthesia and a similar period before the end of the study. Only one subject showed a reduction of rib cage and abdominal volume. Eleven subjects had an increase in abdominal volume in the range 25–250 ml (mean increase 120 ml) (fig. 7). The mean change in chest volume for all the subjects was a decrease of 29 ml. An example of a typical trace is shown in figure 8 where the changes in trunk, rib cage and abdominal volume before, during and after the induction of anaesthesia are illustrated. An increase in end-expiratory rib cage and abdominal volume was seen during manual ventilation following apnoea induced by thiopentone. Subsequently there was a decrease in end-expiratory lung volume to just below control value and then, by the time that the study was discontinued, there was an increase in

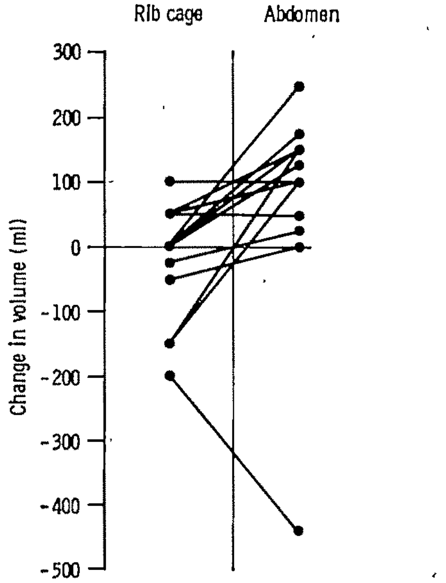

FIG. 7. The change in end-expiratory volume of rib cage and abdomen/diaphragm is the difference between the awake control value and the value obtained during steady-state halothane anaesthesia in the same posture.

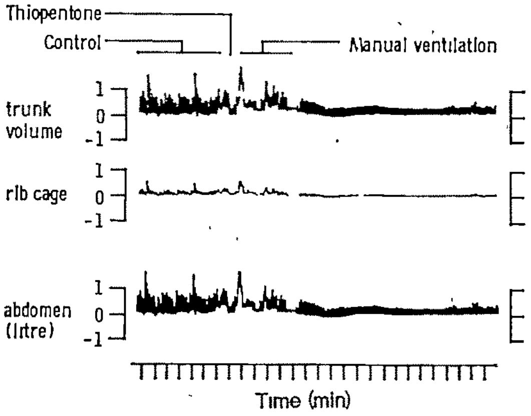

FIG. 8. After 20 min of anaesthesia this patient showed an increase in abdominal volume of 150 ml and an increase in rib cage volume of less than 50 ml while halothane anaesthesia was maintained at an alveolar concentration of 1.0%. Note the change in end-expiratory lung volume just before and during induction of anaesthesia. The change in rib cage position is less than that of the abdomen/diaphragm during these manoeuvres, indicating the differences in elastic properties of these two components of the chest wall.

volume of the abdomen of 150 ml while the rib cage showed a small increase of about 50 ml. The study terminated just before the commencement of surgery.

DISCUSSION

This study has shown that halothane anaesthesia depressed the amplitude of rib cage and diaphragm movements in all the patients investigated. In nine of the 12 patients this effect was most marked on the rib cage contribution, there being a disproportionately large degree of depression of phasic intercostal movement compared with that of the diaphragm. Halothane not only affected the amplitude of phasic movements of the rib cage, but also influenced the tone of the intercostal muscles, impairing rib cage stability and predisposing to paradoxical ventilation. These results are similar to those found by Tusiewicz, Bryan and Froese (1977); however, three of our patients did not show a disproportionate depression of phasic rib cage contribution, which was a consistent finding in all the subjects described by Tusiewicz. This lack of selective depression on rib cage could not be attributed to the much greater range of rib cage contribution in our subjects before anaesthesia. Patients with very small pre-anaesthetic contributions of the rib cage also showed profound depression of phasic intercostal activity with halothane. Goldman (1974) has pointed out that in the upright position a large part of the rib movement results from the mechanical coupling between the diaphragm and the rib cage, so that movement of the latter is simply a result of contraction of the diaphragm alone. As discussed by Tusiewicz, Bryan and Froese (1977), this coupling is less effective in the supine position, but there may be anatomical variations in the attachment of the diaphragm to the rib cage which may explain the unusual features seen in our three patients. These patients also had the largest reduction in tidal volumes and correspondingly large increases in frequency. Wade (1954) and Agostoni and Torri (1967) showed that increasing the frequency of breathing in conscious man produced either no change or a slight reduction in rib cage amplitude, although this may have little relevance to rib cage movement during anaesthesia.

The depressant effects of volatile anaesthetic agents on phasic movements of the chest wall are well recognized (Miller, 1925; Burstein, 1942) and have hitherto been believed to result from supraspinal effects of anaesthetics involving depression of medullary control. Tusiewicz, Bryan and Froese (1977) suggested that the major component of ventilatory depression resulted from preferential suppression of intercostals similar to that seen in the present study. The sensitivity of the "respiratory system" to the depressant effects of volatile anaesthetic agents varies widely.

For example, 3 MAC of ether is required to give the same degree of carbon dioxide retention as 1 MAC of halothane (Larson et al., 1969). The magnitude of the selective effect of different anaesthetic agents on the rib cage has not been studied and it would be of considerable interest to see if depression of rib cage movement has a greater range of susceptibility to different anaesthetics as does depression of movement of the whole chest wall.

Changes in tone of the rib cage musculature were deduced from the changes observed with manual ventilation and from the observation of paradoxical ventilation where the rib cage contribution became negative in sign. During passive ventilation there was a much larger fractional movement of the rib cage than during spontaneous ventilation, although the abdomen/diaphragm movement was always greater than rib cage movement. This increase in rib cage movement, which was noted with thiopentone anaesthesia, showed a further increase following neuromuscular blockade with suxamethonium and this indicated a greater degree of background tone in the rib cage musculature than in the musculature of the abdomen/diaphragm. The relative movements of the rib cage and abdomen/diaphragm under these circumstances were indicative of the relative compliances of these two parts of the chest wall, although regional differences in lung recoil pressure reduced the evenness of distending pressures on the rib cage and abdomen/diaphragm. It is of interest that, whereas the lowest compliances were found in the two oldest subjects, there was no correlation between age and relative rib cage compliance. These results are similar to those described by Grimby, Hedenstierna and Löfström (1975), although these workers reported a larger mean rib cage contribution of 40% of tidal volume awake and, following anaesthesia with thiopentone, fentanyl and mechanical ventilation, there was a much larger rib cage contribution (72%). These workers used the magnetometer technique to record the changes in antero-posterior diameter of the rib cage and abdomen at two points and we have previously suggested (Faithfull, Jones and Jordan, 1979) that this technique may be inaccurate during anaesthesia because of the loss of stability of chest wall shape. The concept of the rib cage as a shell-like structure stabilized by the postural activity of its musculature has been developed by DaSilva and others (1977). They showed in the lightly anaesthetized, prone cat that transition from spontaneous respiration to mechanical ventilation following administration of gallamine was accompanied by a marked change in the shape of the rib cage and abdomen. Furthermore, the range of movement of the rib cage during mechanical ventilation was less than that during spontaneous ventilation, indicating a reduction in rib cage compliance in this posture. While our results, indicating a relative increase in rib cage compliance with neuromuscular blockade, are in agreement with those of Grimby, Hedenstierna and Löfström (1975), the difference in magnitude may be methodological in origin, since the reduction in rib cage compliance in the prone, paralysed cat (DaSilva et al., 1977) may be a result of the greater traction on the rib by the poorly supported abdominal contents. Underestimation of rib cage compliance may also have been produced by displacement of blood from the chest as airway pressure was increased. In the present study, this was observed in the rib cage trace when manual ventilation at a maintained positive airway pressure gave an initial increase followed by a decrease in rib cage volume as blood was displaced. This was followed by an increase in volume of the rib cage to a stable position as the circulation readjusted.

The onset of and recovery from anaesthesia was usually associated with transient and often large phase differences between rib cage and abdominal movement and these disappeared with either return of consciousness or the maintenance of "steady-state" anaesthesia. During the latter stage the consistent diminution in rib cage contribution in most patients was accompanied by a normal in-phase relationship between rib cage and abdomen. However, in two subjects, movements of the rib cage and abdomen were 180° out of phase during deep anaesthesia, producing a negative rib cage contribution. This phase reversal was accentuated by resistive loading in three other patients who had shown neither phase shift nor reduction in rib cage contribution while breathing against the same load before induction of anaesthesia. In the study of Tusiewicz, Bryan and Froese (1977), while none of the five young tracheally intubated patients showed any tendency to a negative rib cage contribution, all three of the non-tracheal intubated adult patients had paradoxical ventilation despite careful adjustment of the lower jaw.

This study has demonstrated that there are two effects of anaesthesia on the function of the rib cage: diminution of ventilatory movement and loss of postural control leading to instability of movement. The mechanism of the selective effect of volatile anaesthetic agents on these two functions of the rib cage is unknown. A helpful analysis of the effects of anaesthesia on these functions of the intercostal muscles has been made by Duron (1973). He classified the chest wall musculature into two groups: (i) the internal and external intercostals, (ii) the diaphragm, interchondral and abdominal muscles. Tonal postural activity predominates in the former group and phasic ventilatory activity in the latter. Movements of these groups are produced by signals fed directly through the alpha motor neurone pathway and indirectly via the gamma loop system, and there is probably a close α–γ linkage which is used in the regulation of muscle function (Sears, 1973). Nathan and Sears (1960) described a temporary paralysis of the diaphragm and intercostals following section of the dorsal cervical and thoracic roots in man and suggested that this resulted from opening of the γ loop. Susceptibility of this α–γ pathway to the effects of halothane has been reported by de Jong, Hershey and Wagman (1967) and it is of interest to note that Duron (1973) showed that muscles with the fewest muscle spindles, and thus least α–γ linkage, are those with the most marked phasic activity. There are few spindles in the diaphragm and interchondral muscles, and their relative lack of inhibition by halothane may result from their independence from γ-loop control. We propose that halothane anaesthesia produces an attenuation of both phasic and tonic acitivity in the intercostal musculature by its predominant effect both on γ efferents and on more central control of α–γ linkage. This leads to reduction in amplitude of phasic movements and loss of tone and also to instability in the shape of the rib cage with paradoxical movements between the rib cage and abdomen/diaphragm, particularly under conditions of increased respiratory loading (T. Sears, personal communication).

Following induction of anaesthesia in man, there is a reduction in functional residual capacity amounting to several hundred millilitre and this is of similar magnitude either with spontaneous respiration or after neuromuscular block (Hewlett et al., 1974a, b). This remarkable finding is so far unexplained. Part of the present study was designed to partition this change in FRC between the rib cage and the abdomen and it was expected that there would be a reduction in rib cage and abdominal volume. We were surprised to find only one subject who showed a reduction of both rib cage and abdominal volume, the majority of subjects showing an increase in abdominal volume (mean change +130 ml) and a small mean decrease in rib cage volume (−29 ml). This discrepancy between the widely reported reduction in internal volume and the net increase in external volume of the trunk found in this study, suggested that the part of the mechanism for the reduction in FRC was an increase in the volume of the abdominal contents which displaces the abdominal wall outwards and the diaphragm upwards into the chest cavity. Such a distortion of the diaphragm into the chest cavity has been reported by Froese and Bryan (1974) from radiographic studies of the position of the diaphragm in awake and anaesthetized man. The only explanation for the increase in abdominal contents is an increase in either abdominal gas or blood volume. An increase in gas volume might occur from diffusion of nitrous oxide into intestinal air pockets and would be quite slow to reach a new equilibrium. A more likely explanation is an increase in vascular volume in the abdomen resulting from either a direct effect of halothane on vascular smooth muscle or impairment of autonomic regulation during anaesthesia. This leads to an augmentation of the normal central shift of blood volume from the legs that produces a gradual reduction of functional residual capacity (FRC) after assuming the supine position (Tenney, 1959). Tenney showed that in conscious subjects this reduction in FRC was accompanied by an increase in abdominal and rib cage circumference, but these changes were absent in four subjects with congenital or traumatic loss of the lower extremities. Lung volume is well controlled in conscious man by adjustments in the tone of the rib cage and abdominal wall musculature, the diaphragm position being controlled to a greater extent by fine control of the musculature of the rib cage and abdominal musculature than by fine adjustments within the diaphragm itself. Thus, following induction of anaesthesia, there is loss of postural reflexes in the antigravity muscles (which include those of the chest wall) and if abdominal pressure increases because of vasodilatation in the viscera, the diaphragm and abdominal wall are displaced in accordance with their respective compliances.

In conclusion, the present study has demonstrated a number of interacting factors that may contribute to the gas exchange abnormality that occurs during anaesthesia. Reduction in amplitude of rib cage movement results in a redistribution of $\dot{V}/\dot{Q}$ ratios within the lung. Loss of chest wall stability enhances this effect by increasing the likelihood of paradoxical ventilation, especially in the presence of obstruction. Increased respiratory frequency and reduction in tidal volume further exacerbates the $\dot{V}/\dot{Q}$ abnormality because of reduced time for diffusive mixing in the airways (Cumming et al., 1967) and for the increased deadspace fraction of inspired gas (Cumming, Jones and Horsfield, 1969; West, 1971). Loss of postural reflexes impairs control of functional residual capacity, leading to a reduction in lung volume and narrowing or closure of dependent airways. These effects can only be ameliorated partially by combining positive end-expiratory pressure with a low inspiratory resistance breathing circuit. Further research into the effects of different anaesthetic agents on the chest wall is required to see if there is a wide difference in selective rib cage depression.

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MOUVEMENT DE LA CAGE THORACIQUE PENDANT UNE ANESTHESIE A L'HALOTHANE CHEZ L'HOMME

RESUME

Le mouvement de la paroi de la poitrine, divisé entre les contributions de la cage thoracique et de l'abdomen/diaphragme, a été mesuré à l'aide de quatre extensiomètres à mercure dans du caoutchouc et d'un ordinateur analogique. La contribution relative du volume de la cage thoracique et de l'abdomen/diaphragme par rapport à la quantité d'air expiré à chaque respiration a été mesurée sur 13 sujets avant et pendant l'anesthésie au thiopentone et à l'halothane. Chez les sujets éveillés, le mouvement de l'abdomen/diaphragme a contribué à plus de 70% de la quantité d'air expiré à chaque respiration, la contribution de la cage thoracique a été moindre et s'est située entre 5 et 30%. La ventilation manuelle pendant l'induction de l'anesthésie a montré que la cage thoracique était moins compliante que l'abdomen/diaphragme, mais après l'administration de suxaméthonium il y a eu une augmentation disproportionnée de la compliance de la cage thoracique. L'anesthésie par l'halothane a résulté, chez neuf sujets sur 12, en une diminution importante de la contribution fractionnelle de la cage thoracique. Chez deux de ces sujets, la respiration a été paradoxale, le mouvement de la cage thoracique et celui de l'abdomen/diaphragme étant déphasés de 180°. Cet effet a facilement été reproduit sur trois autres sujets en insérant une résistance (1 kPa litre^{-1} s) dans le circuit de l'anesthésie. Cette technique a aussi donné des informations sur les variations du volume du tronc causées par l'anesthésie. Onze sujets ont accusé une augmentation du volume abdominal expiratoire final (augmentation moyenne de 120 ml) pendant l'anesthésie par l'halothane,

alors qu'il y avait une réduction moyenne de 29 ml dans le volume expiratoire final de la cage thoracique. Nous en avons conclu que l'halothane déprime à la fois l'activité tonique et l'activité de phase du réflexe postural, ce qui a surtout affecté la musculature de la cage thoracique. Ceci a réduit l'amplitude du mouvement de phase de la cage thoracique, a affecté la stabilité de la cage thoracique et l'a prédisposée à la ventilation paradoxale. Les résultats laissent aussi penser que la réduction du volume pulmonaire pendant l'anesthésie peut provenir de la perte de contrôle postural de la paroi de la poitrine et un déplacement central du volume de sang.

BRUSTKORBBEWEGUNG WÄHREND HALOTHANNARKOSE BEIM MENSCHEN

ZUSAMMENFASSUNG

Brustwandbewegungen, geteilt in Bewegungen von Brustkorb und Unterleib/Zwerchfell, wurden mit vier Quecksilber-Gummi-Messgeräten und mit einem Analogkomputer gemessen. Die relativen Volumsbeiträge von Brustkorb und Unterleib/Zwerchfell zum Atemvolumen wurden bei 13 Personen vor und nach Thiopenton- und Halothannarkose gemessen. Bei wachen Personen trug die Unterleibs/Zwerchfell-Bewegung mehr als 70% des Atemvolumens bei, die Brustkorbbewegung nur von 5 bis 30%. Manuelle Beluftung während des Einleitungsstadiums der Narkose zeigte eine geringere Biegsamkeit des Brustkorbs gegenüber Unterleib/Zwerchfell, aber bei Verabreichung von Suxamethonium gab es einen unverhältnismässigen Anstieg der Brustkorbbiegsamkeit. Bei neun von 12 Personen führte die Halothannarkose zu einer starken Beitragsverringerung durch den Brustkorb. Bei zwei dieser Personen kam es zu paradoxer Atmung, wobei die Bewegungen von Brustkorb und Unterleib/Zwerchfell um 180° phasenabweichend waren. Dieser Effekt konnte bei drei anderen Personen leicht durch Einführung eines Widerstandes (1 kPa Liter^{-1}) in die Narkoseleitung erzielt werden. Diese Methode ergab auch Informationen über Volumsveränderungen des Rumpfes durch Narkose. Elf Personen zeigten einen Anstieg des Endausatmungs–Unterleibsvolumens (mittlerer Anstieg 120 ml) wahrend der Halothannarkose, sowie eine mittlere Verringerung des Endausatmungs–Brustkorbvolumens von 29 ml. Daraus schlossen wir, dass Halothan sowohl die phasische als auch die tonische Reflexaktivität unterdrückt, wodurch hauptsächlich die Brustkorbmuskulatur betroffen wurde. Dadurch wird die Amplitude der phasischen Brustkorbbewegung verringert, die Stabilität des Brustkorbs beeinträchtigt und dieser für paradoxe Atmung anfällig gemacht. Die Resultate zeigen ferner, dass die Verringerung des Lungenvolumens während der Narkose ein Ergebnis eines Verlustes an Haltungskontrolle des Brustkorbes sowie einer zentralen Verschiebung des Blutvolumens sein könnte.

MOVIMIENTO DEL COSTILLAJE DURANTE ANESTESIA DE HALOTANO EN EL HOMBRE

SUMARIO

Se midió el movimiento de las paredes del pecho, distinguiéndose las contribuciones del costillaje y abdomen/diafragma, empleándose para tal fin cuatro deformímetros de "mercurio en caucho" y un computador analógico. La contribución de volumen relativa del costillaje y del abdomen/diafragma al volumen de respiracíon corriente fue medida en 13 sujetos antes y durante anestesia con tiopentona y halotano. En los sujetos despiertos, el movimiento del abdomen/diafragma contribuyó más de 70% del volumen de la respiración y la contribución menor del costillaje varió entre 5 y 30%. La ventilación manual durante la inducción de anestesia indicó que el costillaje era menos elástico que el abdomen/diafragma, pero cuando se administró suxametonio, se produjo un aumento desproporcionado en la elasticidad del costillaje. En neuve de 12 sujetos, la anestesia de halotano causó una gran disminución en la contribución fraccional del costillaje. En dos de estos sujetos se produjo una respiración paradójica, estando el movimiento del costillaje y del abdomen/diafragma defasado en 180°. Este efecto fue producido con facilidad en tres sujetos más mediante la inserción de una resistencia (1 kPa litro^{-1}) en el circuito anestésico. La técnica también aportó información acerca de los cambios en el volumen del tronco inducidos por anestesia. Once sujetos acusaron un aumento en el volumen abdominal al final de la expiración (aumento medio de 120 ml) durante la anestesia de halotano, mientras que se produjo una reducción media en el volumen del costillaje al final de la expiración de 29 ml. Concluímos que el halotano deprimió la actividad refleja, tanto fásica como tónica, que afectó predominantemente a la musculatura del costillaje. Esto redujo la amplitud del movimiento fásico del costillaje, prejudicó la estabilidad del costillaje y predispuso la ventilación paradójica. Los resultados también sugirieron que la reducción en el volumen de los pulmones durante la anestesia puede ser el resultado de una pérdida de control de la postura en la pared del pecho y un desplazamiento central del volumen sanguíneo.

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HAEMODYNAMICS OF CARDIAC TAMPONADE DURING VARIOUS MODES OF VENTILATION

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SUMMARY

Cardiac output and pleural, pericardial, arterial and cardiac pressures were measured in baboons during different modes of ventilation in the presence of acute cardiac tamponade. Fluctuations in pleural pressure during intermittent positive pressure ventilation were transmitted to the pericardial fluid. Cardiac output and transmural right ventricular end-diastolic pressure were significantly greater during spontaneous ventilation than during intermittent positive pressure ventilation with or without positive end-expiratory pressure. It is recommended that a patient undergoing surgery for cardiac tamponade be allowed to breathe spontaneously until the chest is opened and the pericardium incised.

The management of ventilation during anaesthesia for surgery of acute cardiac tamponade remains controversial. Stanley and Weidauer (1973) noted that positive pressure ventilation decreases cardiac output and they advocated drainage of the cardiac tamponade under local anaesthesia before general anaesthesia is induced. This view is supported by Kaplan, Bland and Dunbar (1976). Branthwaite (1977) suggested that controlled ventilation has little effect on pre-existing large pericardial pressures and that it improves cardiac output by increasing pulmonary wedge pressure and augmenting left ventricular filling.

As traumatic cardiac tamponade is relatively common in our group of hospitals, it was decided to compare the effects of spontaneous ventilation, intermittent positive pressure ventilation (IPPV) and intermittent positive pressure ventilation with positive end-expiratory pressure (PEEP) on the haemodynamic state of experimental animals with cardiac tamponade.

METHODS

Five male Cape Chacma baboons (*Papio ursinus*) (weight 26–28 kg) were anaesthetized with phencyclidine 2 mg kg^{-1} i.m. and anaesthesia was maintained with an i.v. infusion of thiopentone 0.06 mg $kg^{-1} min^{-1}$. A cuffed tube was inserted into the trachea and ventilation controlled with room air using a model 607 Harvard Animal Respirator to maintain normal arterial blood-gas tensions.

Two catheters (2 mm i.d. with terminal and lateral holes) were placed in the pericardial cavity via a left anterior thoracostomy and secured with purse-string sutures to seal the pericardium. The catheters were brought out through the thoracotomy wound and the chest closed in layers. A pleural drain was inserted and connected to an underwater seal. Pericardial pressure was measured via one of the catheters, while the other was used to introduce saline into the pericardial cavity.

Central venous, pulmonary artery and pulmonary capillary wedge pressures were measured with an Edwards Swan–Ganz thermodilution catheter (93A–118–7F) introduced through either a brachial or a femoral vein so that the proximal lumen was situated in either the superior or the inferior vena cava. Cardiac output was measured with the same catheter and a model 9510 Edwards cardiac output computer using an injectate of 5 ml of 5% dextrose in water at 0–2 °C. For each steady state the cardiac output was measured three times and the mean calculated. The right ventricle and right atrium were catheterized separately via the femoral veins and the left ventricle via the left femoral artery. Systemic arterial pressure was measured in the right femoral artery. A saline-filled catheter (1 mm i.d. with multiple side holes) was introduced percutaneously into the right pleural cavity to measure pleural pressure.

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All pressures were related to the mid-axillary line. Arterial, left ventricular and right ventricular pressures were measured with Statham P 23 AA transducers; pleural, pericardial, pulmonary arterial, right atrial and central venous pressures with Statham P 23 BB transducers. E.c.g. and vascular pressures were recorded on a Beckman 8-channel Dynagraph model R511. The pressure transducers and recorder were calibrated using a mercury manometer and the calibrations checked immediately before each recording by simultaneously loading all the transducers with a water manometer calibrated in mm Hg. As more than eight measurements were obtained, recordings were made in two runs. The first run included central venous, pulmonary artery and left ventricular pressures, and the second included right atrial, pulmonary capillary wedge and femoral artery pressures. Thus central venous and right atrial pressures were measured with the same transducer while pulmonary artery and pulmonary capillary wedge pressures were paired similarly, as were left ventricular and femoral artery pressures. E.c.g. and respiratory traces which were recorded in both runs were used to ensure the recordings were in phase.

When all the catheters were in place, heparin 2 mg kg^{-1} was given i.v. The baboon was then allowed to breathe spontaneously for 15 min, pressures were recorded and the cardiac output measured (fig. 1). Saline at 37 °C was introduced into

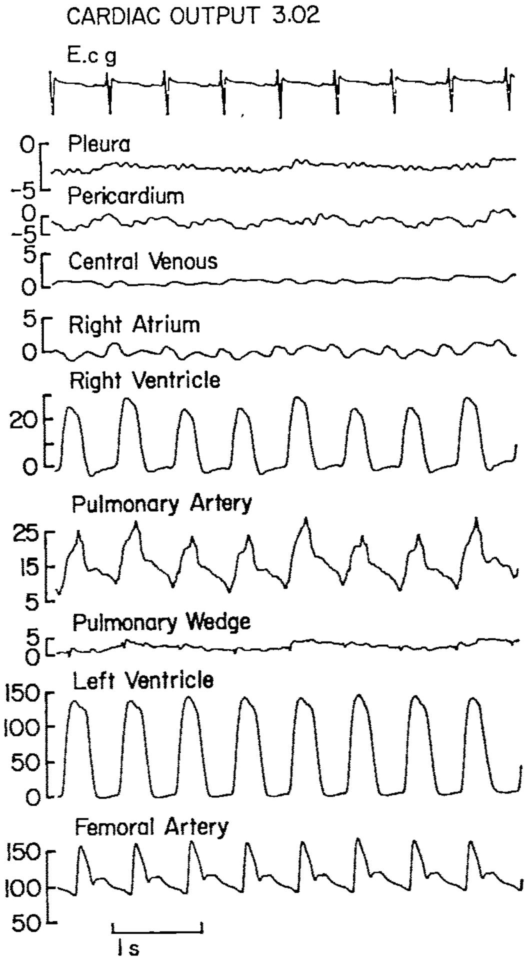

FIG. 1. Cardiac output (litre min^{-1}), e.c.g. and pressure tracings (mm Hg) from a typical experiment before cardiac tamponade was produced.

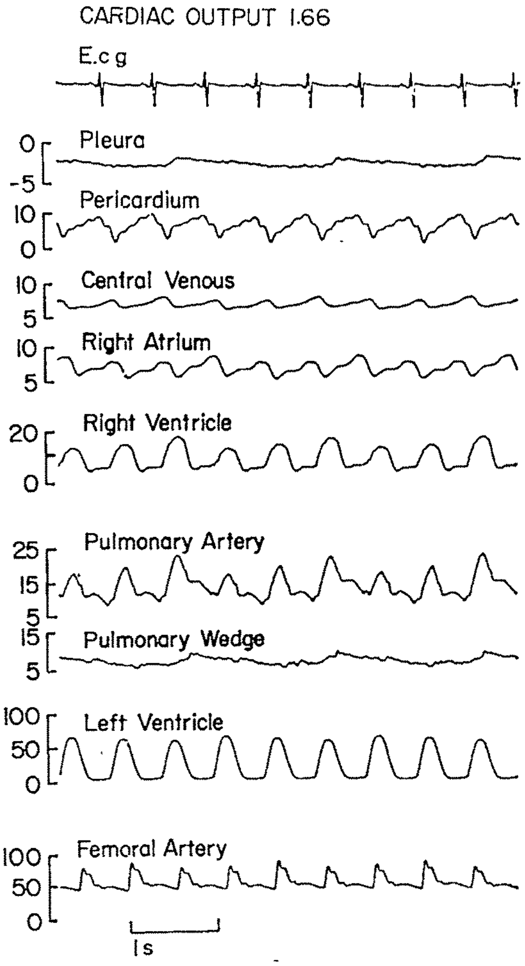

FIG. 2. Cardiac output (litre min^{-1}), e.c.g. and pressure tracings (mm Hg) with cardiac tamponade and spontaneous ventilation.

the pericardial cavity in 25-ml increments and the pericardial pressure was measured 2 min after each increment.

Saline was added until pulsus paradoxus appeared and arterial systolic pressure was reduced to 50–60% of the control value. Fifteen minutes after inducing the tamponade, pressures were recorded and the cardiac output measured (fig. 2). The lungs were then ventilated and recordings taken after 15 min (fig. 3). The final recordings were taken after 15 min of ventilation with PEEP of 10 cm H_2O (fig. 4) and the baboon was sacrificed at the conclusion of these recordings. In one experiment 25-ml increments of saline were withdrawn from the pericardial cavity during spontaneous ventilation and the pericardial pressure measured 2 min after each withdrawal.

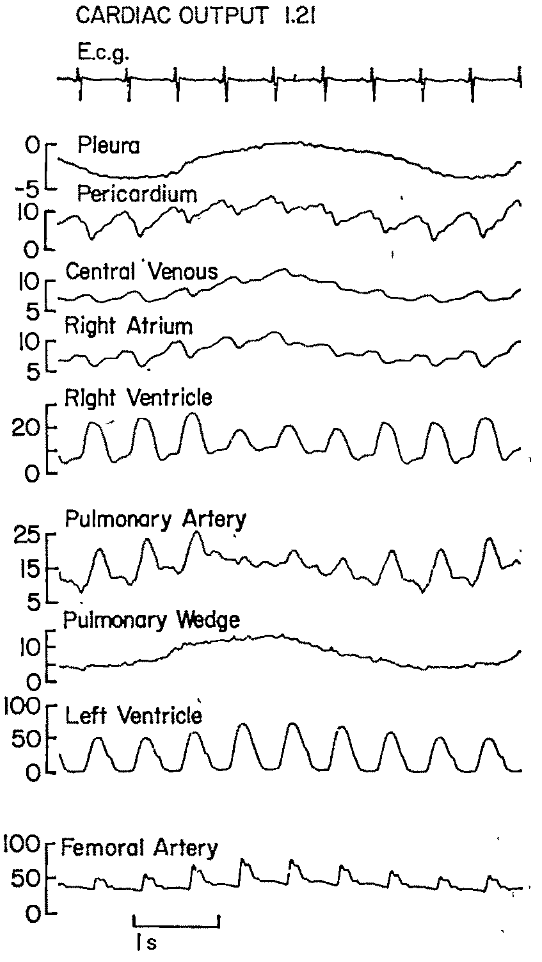

FIG. 3. Cardiac output (litre min^{-1}), e.c.g. and pressure tracings (mm Hg) with cardiac tamponade and IPPV.

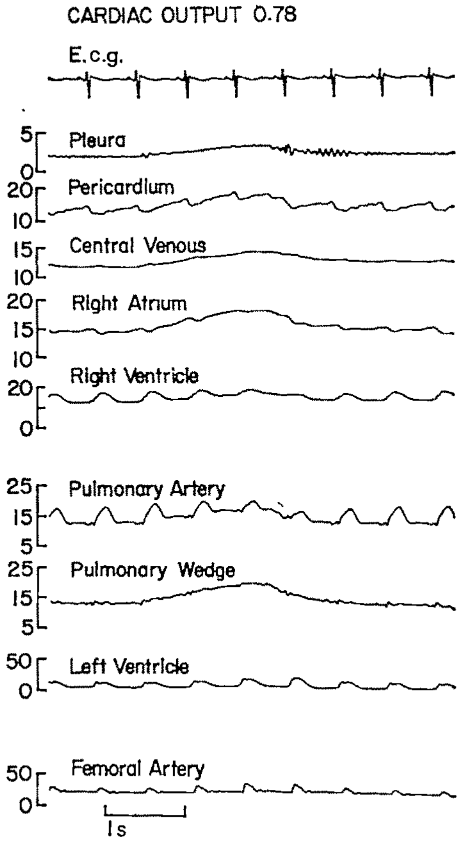

FIG. 4. Cardiac output (litre min^{-1}), e.c.g. and pressure tracings (mm Hg) with cardiac tamponade and IPPV with PEEP.

Mean pressures were derived from the recordings by integration of the traces over a complete respiratory cycle. Mean pressures during inspiration and expiration were obtained by integration over two cardiac cycles at mid-inspiration and mid-expiration respectively. The integrations were performed with a Hewlett-Packard HP-67 calculator.

Linear regressions, means and standard errors were calculated by standard statistical techniques, and the significance of differences was calculated using the paired *t* test. An unpaired *t* test was used to compare the slopes of the regression lines (Armitage, 1971).

RESULTS

Addition of saline to the pericardial cavity increased the pericardial pressure but the pressure–volume curves vary considerably (fig. 5). In general the curves increase sharply initially, become less steep at intermediate volumes and increase rapidly at

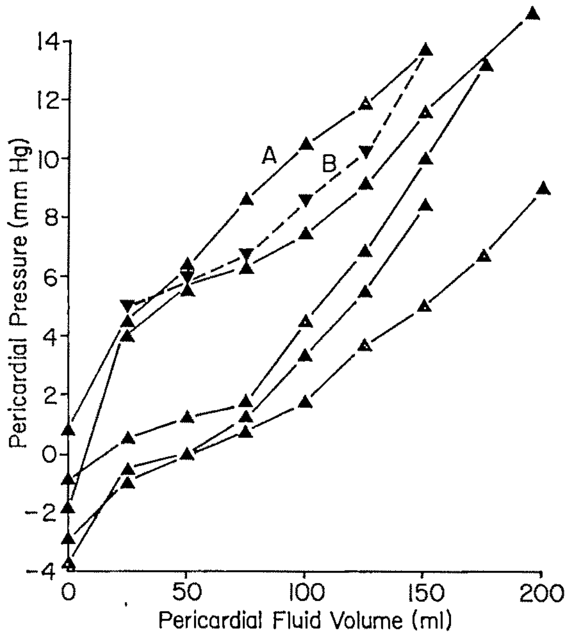

FIG. 5. Individual pericardial pressure–volume curves of five baboons. A and B refer to the same animal. ▲ = increasing volumes; ▼ = decreasing volumes.

high volumes. Moderate tamponade, indicated by tachycardia, arterial hypotension with pulsus paradoxus and increased central venous pressure, occurred at pericardial pressures of 9–12 mm Hg. Hysteresis was present in the pressure–volume curve produced by withdrawing saline, but the differences in pressure between infusion and withdrawal curves did not exceed 2 mm Hg (0.27 kPa).

The changes during cardiac tamponade are summarized in figure 6. Cardiac tamponade increased heart rate and caused a significant decrease in arterial pressure. Pulsus paradoxus developed and vasoconstriction became apparent. The mean pulmonary artery and pleural pressures were unchanged while central venous, right atrial, pulmonary wedge, right ventricular end-diastolic (RVED) and pericardial pressures were significantly increased. Mean transmural RVED pressure (mean RVED pressure minus mean pericardial pressure) and cardiac output were both decreased significantly. IPPV caused a further significant decrease in both transmural RVED pressure and cardiac output. Pericardial and pulmonary artery pressures were both increased while changes in the other pressures measured were not significant. The introduction of PEEP decreased cardiac output further and caused a non-significant increase in all the pressures except the systemic arterial pressure, which decreased.

During tamponade, pericardial pressure fluctuations were significantly related to the pleural pressure changes with respiration during both spontaneous ventilation and IPPV, but the slopes of the relationships differed ($P < 0.01$) (fig. 7).

DISCUSSION

The pericardial pressure–volume relationship and hysteresis described here is similar to that shown by Morgan, Guntheroth and Dillard (1965) in dogs of about the same weight as the baboons used in the present study. This hysteresis and the steepness of the curves explain the clinical improvement that follows the removal of a small volume of pericardial fluid from a patient with cardiac tamponade (Kaplan, Bland and Dunbar, 1976).

The haemodynamic changes induced by cardiac tamponade in this study did not differ from those described by previous authors. The further decrease in cardiac output caused by the introduction of IPPV is of clinical significance and supports the view of Stanley and Weidauer (1973) that positive pressure ventilation should be avoided in the presence of cardiac tamponade. This decrease in cardiac output is probably secondary to the decrease in the transmural RVED pressure (decreased right ventricular preload) which results in a decreased output from the right ventricle followed by a decrease in left ventricular output as the return to the left side of the heart decreases. This mechanism is consistent with the finding of Guntheroth, Morgan and Mullins (1967) that the left ventricular stroke volume is dependent on the right ventricular stroke volume one or two beats earlier.

As cardiac output is decreased further when PEEP is added to IPPV, this mode of ventilation also should be avoided in the presence of cardiac tamponade. Although the present data give little indication of the mechanism of this decrease, it is likely to be caused by a further decrease in both the venous return and the transmural RVED pressure (Qvist et al., 1975).

The finding that positive pressure changes in the pleural cavity are transmitted faithfully to the fluid in the pericardial cavity is contrary to the idea of Branthwaite (1977) and supports the concept of a decreased transmural RVED pressure being part of the mechanism responsible for the decreased cardiac output. It is interesting that negative changes in pleural pressure are not well transmitted to the tamponade fluid. This is probably because the

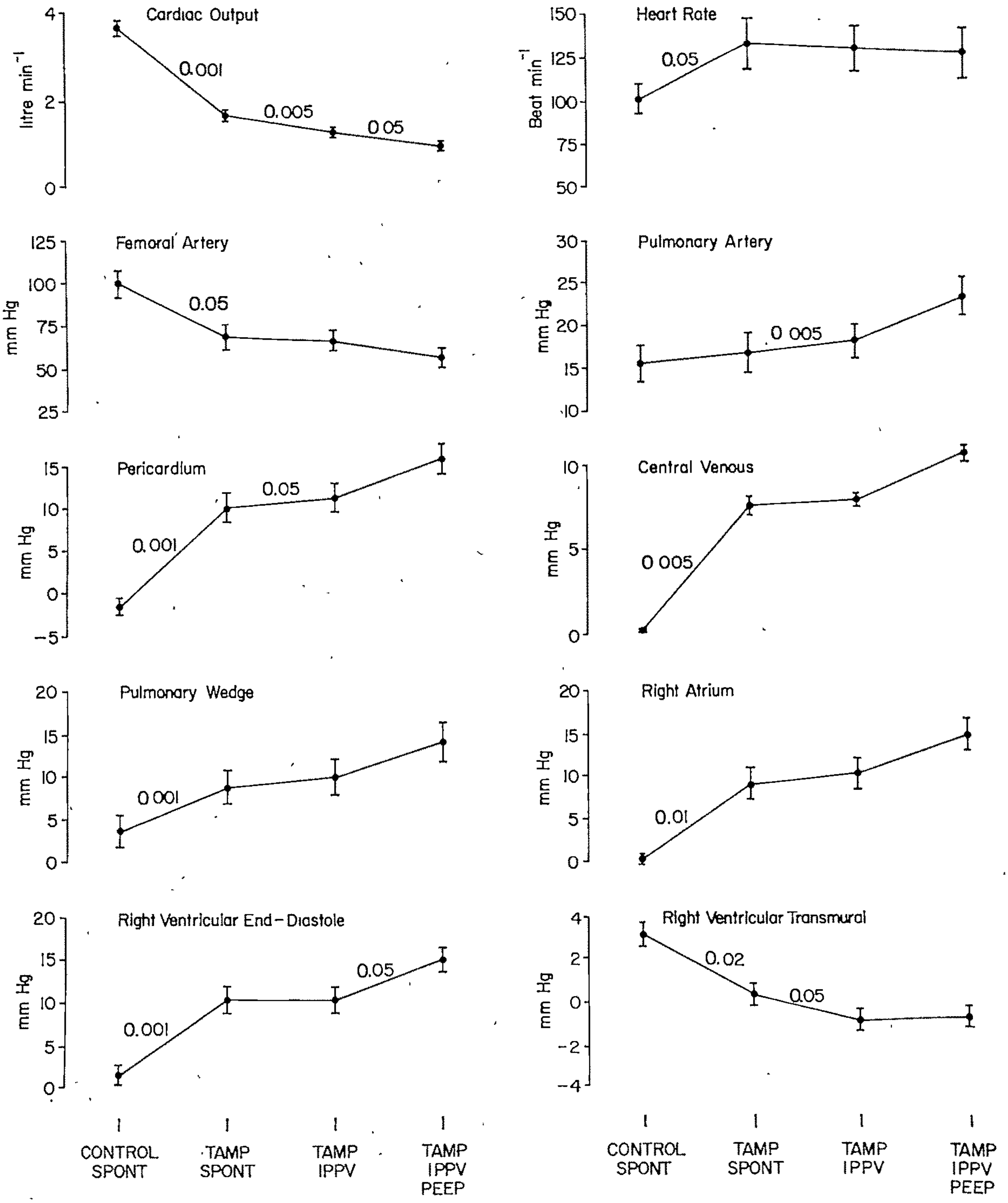

FIG. 6. Mean (±SEM) values of measurements during the control period and during cardiac tamponade with different modes of ventilation. Significant differences based on paired *t* tests are indicated. Pressures are mean pressures over a complete respiratory cycle. TAMP = tamponade; SPONT = spontaneous ventilation; IPPV = intermittent positive pressure ventilation; PEEP = positive end-expiratory pressure.

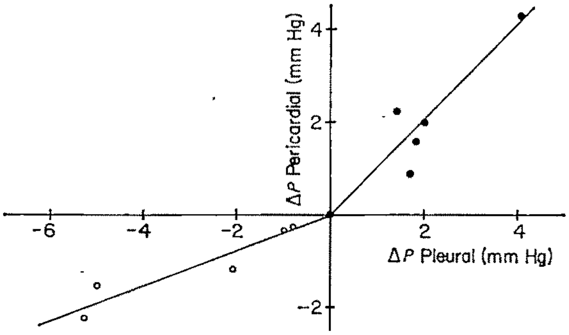

FIG. 7. Relationship of pressure differences (ΔP) between maximum inspiration and expiration in the pericardial and pleural cavities of five baboons during spontaneous ventilation (open circles: $y = 0.37x - 0.05$, $r = 0.957$, $P < 0.01$) and IPPV (solid circles: $y = 1.08x - 0.08$, $r = 0.935$, $P < 0.01$) in the presence of cardiac tamponade.

relatively inelastic, fibrous pericardium, once fully distended, allows very little further expansion when the surrounding pressure is reduced. It is thus unlikely that negative end-expiratory pressure ventilation would have much advantage over IPPV alone.

It is concluded that the use of PEEP in the presence of cardiac tamponade is contraindicated and that IPPV should be avoided. If it is not possible to perform a pericardiocentesis before the induction of general anaesthesia or if the tamponade fluid reaccumulates rapidly after removal (as is often the case with traumatic tamponade), spontaneous ventilation should be maintained for as long as possible after the induction of anaesthesia. Positive pressure ventilation should be instituted only when the chest is opened and drainage of the pericardial cavity is imminent. In view of the desirability of tracheal intubation in patients with cardiac tamponade the possibility of intubation under topical anaesthesia should be considered.

ACKNOWLEDGEMENTS

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HEMODYNAMIQUE DU TAMPONNEMENT DU CŒUR AU COURS DE DIVERS MODES DE VENTILATION

RESUME

Le débit cardiaque et les pressions pleurales, péricardiques, artérielles et cardiaques ont été mesurées sur des babouins au cours de divers modes de ventilation en présence d'un tamponnement aigü du cœur. Les fluctuations de la pression pleurale au cours de la ventilation sous pression positive intermittente ont été transmises au fluide péricardique. Le débit cardiaque et la pression diastolique finale transmurale ventriculaire droite ont été sensiblement plus forts pendant la ventilation spontanée que pendant la ventilation sous pression positive intermittente avec ou sans pression positive expiratoire finale. Il est recommandé que les malades soumis à une intervention chirurgicale pour tamponnement du cœur soient autorisés à respirer spontanément jusqu'à ce que la poitrine ait été ouverte et que le péricarde ait été incisé.

HÄMODYNAMIK VON KARDIALTAMPONADE WÄHREND VERSCHIEDENER BELÜFTUNGSMETHODEN

ZUSAMMENFASSUNG

Herzminutenvolumen, sowie pleuraler, perikardialer, arterieller und kardialer Druck wurde bei Pavianen während verschiedener Methoden von Belüftung bei Vorhandensein einer akuten Kardialtamponade gemessen. Fluktuierungen des Pleuraldruckes bei intermittierender positiver Druckbelüftung wurden an die Perikardialflüssigkeit weitergeleitet. Herzminutenvolumen und der transmurale enddiastolische Druck im rechten Ventrikel waren wesentlich höher als bei intermittierender positiver Druckbelüftung mit oder ohne positiven Endausatmungsdruck. Es wird empfohlen, einem Patienten bei chirurgischem Eingriff für Kardialtamponade spontane Atmung zu gestatten, bis der Brustraum geöffnet und der Einschnitt ins Perikardium vorgenommen wurde.

HEMODINAMICA DEL TAPONAMIENTO CARDIACO DURANTE DIVERSOS MODES DE VENTILACION

SUMARIO

Se midió el volumen-minuto cardíaco y las presiones pleural, pericardial, arterial y cardíaca en babuinos durante diferentes modos de ventilación en la presencia de un taponamiento cardíaco agudo. Las fluctuaciones en la presión pleural durante la ventilación de presión positiva intermitente fueron transmitidas al fluido pericardial. El volumen-minuto cardíaco y la presión transmural del ventrículo derecho al final del diástole fueron significativamente mayores durante la ventilación espontánea que durante la ventilación de presión positiva intermitente con o sin presión positiva al final de la expiración. Se recomienda permitirle respirar espontáneamente a un paciente sometido a cirugía de taponamiento cardíaco hasta que se abra el pecho y se corte el pericardio.

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MUTAGENICITY OF INHALATION ANAESTHETICS: TRICHLOROETHYLENE, DIVINYL ETHER, NITROUS OXIDE AND CYCLOPROPANE*

J. M. BADEN, M. KELLEY, R. I. MAZZE AND V. F. SIMMON

SUMMARY

The mutagenic potential of trichloroethylene, divinyl ether, nitrous oxide and cyclopropane was assessed *in vitro* by microbial assay employing two histidine-dependent strains of *Salmonella typhimurium*, TA1535 and TA100. Anaesthetic agents in various concentrations were incubated with bacteria in the presence or absence of an enzyme system prepared from enzyme-induced rat liver. Nitrous oxide and cyclopropane were not mutagenic, whereas divinyl ether gave a strongly positive response. Results for trichloroethylene were equivocal. These and previous studies with the salmonella system, together with mutagenicity studies using different test systems, indicate that modern inhalation anaesthetic agents are unlikely to be mutagenic.

Among the suggested hazards of operating room contamination by anaesthetic gases is an increased frequency of malignancies in female anaesthetists (Cohen et al., 1974). It is therefore appropriate to screen the anaesthetic agents for possible carcinogenic potential. The salmonella–microsome test (Ames, McCann and Yamasaki, 1975) is an assay that has proved useful in the detection of chemical carcinogens as mutagens. We used this procedure to test halothane, and four halogenated ethers—methoxyflurane, isoflurane, enflurane and fluroxene (Baden et al., 1976, 1977)—for mutagenic activity; only fluroxene (2,2,2-trifluoroethyl vinyl ether) was mutagenic (Baden et al., 1978). In the present study we have tested the volatile anaesthetics trichloroethylene and divinyl ether and the gaseous anaesthetics, nitrous oxide and cyclopropane, to determine their mutagenic potential.

METHODS

The methods and materials used for testing anaesthetic agents in the salmonella assay system have been reported in detail elsewhere (Baden et al., 1976) and are summarized below. The anaesthetics tested were commercially available preparations. Trichloroethylene and divinyl ether were greater than 99.5% pure as assayed by gas chromatography.

Bacterial preparation

Two histidine-dependent strains of *Salmonella typhimurium*, TA1535 and TA100, were used (Ames, McCann and Yamasaki, 1975). For each experiment, inocula from stock cultures grown overnight at 37 °C were used in a nutrient broth.

Metabolic system

A mammalian metabolic activation system, S-9 mix, was prepared from the livers of male Sprague–Dawley rats sacrificed 5 days after i.p. injection of 500 mg kg^{-1} of Aroclor 1254, a polychlorinated biphenyl. Aroclor is a potent inducer of the mixed-function oxidase system. Each assay was conducted both with and without the metabolic activation system.

Desiccator incubation experiments

Bacteria-seeded glucose-minimal plates with or without S-9 mix were placed in 9-litre, air-tight desiccator jars. Liquid or gas volumes of anaesthetics were added to the desiccators to give desired concentrations, which were verified at the beginning and end of exposure using an infra-red gas analyser. The concentrations, ±10% tolerance, ranged from 0.1 to

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30% for divinyl ether, 0.1 to 10% for trichloroethylene and 1 to 81% for nitrous oxide and cyclopropane. The concentrations did not change significantly with time. Vinylidene chloride 3% was used as a positive control. The bacterial plates were exposed to the test compound in sealed desiccator jars for 8 h at 37 °C then the plates were removed from the desiccators and incubated for a further 40 h at 37 °C. Colonies on each plate were counted. Triplicate plates were prepared at each test concentration, and each experiment was performed at least twice.

Liquid incubation experiments

Bacterial cells, with or without S-9 mix, and various amounts of test chemical were added to sterile, 15-ml stoppered tubes and rotated on a wheel for 2 h at 37 °C. The air phase concentrations for a particular anaesthetic, in the air spaces above the reaction mixtures, were the same as those used in the desiccator experiments. Concentrations were measured at the beginning and end of exposure, using an infra-red gas analyser, and were found to vary by not more than 10% with time. Aliquots of the test sample were added to tubes of top agar, mixed and poured onto glucose-minimal medium plates. 2-Anthramine 2.5 µg per plate was used as a positive control. The plates were incubated for 2 days at 37 °C in air and colonies were counted. Triplicate plates were prepared at each test concentration, and each experiment was performed at least twice.

Chemicals

The source and purity of chemicals were as follows: trichloroethylene, Aldrich Chemical Co. (Milwaukee, Wisconsin), 99%—contains no trace of 1-2 epoxybutane or epichlorohydrin; divinyl ether, Marshallton Chem. Co. (Winston, Salem, N.C.) 99.9%; nitrous oxide, Liquid Air, Inc. (San Francisco, California), 99%; cyclopropane, Liquid Carbonic (San Carlos, California), 99.9%.

Analysis of data

The numbers of revertant colonies on treated plates were compared with the numbers of spontaneous revertant colonies on plates exposed to room air. Statistical analysis was by *t* test; $P<0.05$ was considered significant.

RESULTS

Nitrous oxide and cycloprane did not increase the number of revertants in strain TA100 when assayed either in desiccators or in liquid incubation (table I). Similar negative results were obtained with strain TA1535. In contrast, plates exposed to the positive controls, vinylidene chloride or 2-anthramine showed 2.4–14.4-fold increases in the number of revertant colonies.

Divinyl ether was mutagenic to strains TA100 and TA1535 in desiccator and liquid incubation. In desiccators, a dose-dependent increase in revertants occurred in the absence of metabolic system at vapour

TABLE I. *Mutagenicity,* Salmonella typhimurium *strain TA*100 (*mean number of revertant colonies per plate* ± *SEM, n* = 6)

		Nitrous oxide		Cyclopropane	
Concn (vol %)		Without S-9	With S-9	Without S-9	With S-9
Desiccator	0	144±16	167±8	167±12	183±16
	1	167±3	177±8	144±11	157±12
	3	158±14	178±18	149±10	157±8
	9	153±7	147±7	166±10	153±10
	27	162±17	155±9	168±8	181±16
	81	144±20	160±10	125±14	122±9
	Vinylidene chloride 3%	669±63	403±34	886±56	604±37
Liquid	0	115±10	117±10	92±1	90±5
	1	104±10	98±11	91±5	84±6
	3	89±6	103±15	91±7	86±3
	9	83±5	110±4	86±2	89±7
	27	98±8	101±8	96±6	86±6
	81	92±9	99±11	91±5	92±7
	2-anthramine 2.5 µg/plate	107±10	1122±93	117±8	1299±166

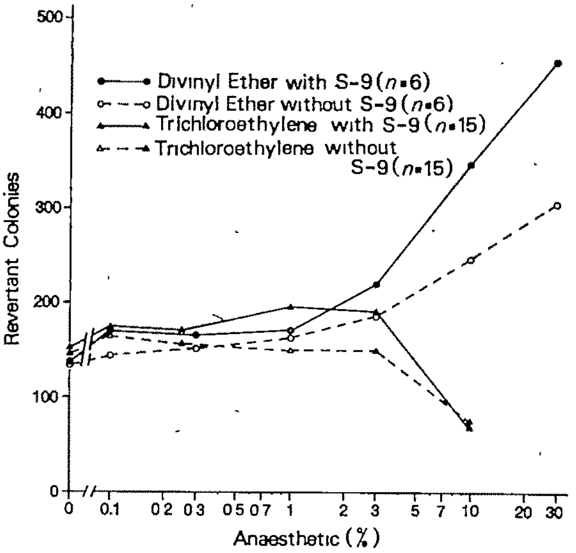


FIG. 1. Revertant colonies of *Salmonella typhimurium*, strain TA100, after desiccator incubation with divinyl ether and trichloroethylene. Divinyl ether produced a dose-dependent increase in the number of revertant colonies at vapour concentrations greater than 1%; the maximum increase above background was 2.5–3.5-fold when S-9 was added. Trichloroethylene produced a 30% increase in the number of revertant colonies only in the presence of S-9.

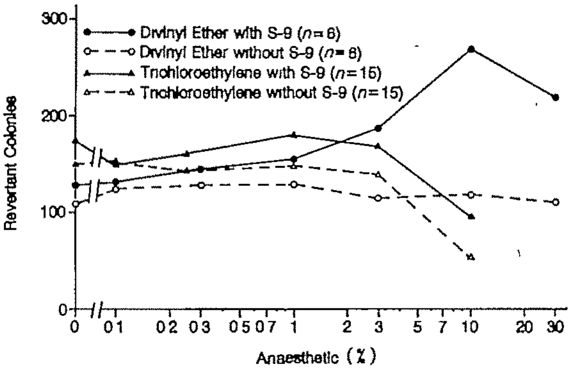


FIG. 2. Revertant colonies of *Salmonella typhimurium*, strain TA100, after liqiud incubation with divinyl ether and trichloroethylene. Divinyl ether produced a dose-dependent increase in the number of revertant colonies in vapour concentrations greater than 1%. The increase was seen only in the presence of S-9 and reached a maximum of 2.5-fold above background. Trichloroethylene did not increase the number of revertants above background.

concentrations greater than 1%; when the metabolic system was added, there was an increase above background of 8–11-fold for TA1535 and 2.5–3.5-fold for TA100. In liquid incubation, a mutagenic response occurred only in the presence of the S-9 mix. Results are shown for strain TA100 in figures 1 and 2.

Trichloroethylene did not increase the number of revertants in strain TA1535 or when assayed by liquid incubation. In desiccators, however, with the metabolic system present, the mean number of revertants of TA100 was increased approximately 30% above background (149 ± 12, $n = 15$) at 1% (196 ± 13, $n = 15$) and 3% (194 ± 6, $n = 15$) vapour concentrations (fig. 1.). These increases were statistically significant ($P < 0.01$).

DISCUSSION

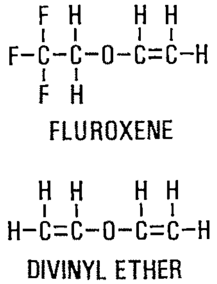
In the present study, the most significant findings occurred with divinyl ether which was mutagenic to both strains of salmonella. Both the gases, nitrous oxide and cyclopropane, were not mutagenic while the results of the trichloroethylene tests were equivocal. In similar studies of halothane, enflurane, methoxyflurane and fluroxene, only fluroxene (2,2,2-trifluoroethyl vinyl ether) was mutagenic (Baden et al., 1978). Fluroxene, however, gave positive results only in liquid incubation, whereas divinyl ether was mutagenic in both liquid and desiccator incubation. In the desiccator assay, divinyl ether was mutagenic without the metabolic systems, although its activity was enhanced when metabolizing enzymes were present. This finding indicates that both divinyl ether and one or more of its metabolic products are mutagenic. In the past it has been assumed that the toxic effects of anaesthetic agents were produced only by reactive anaesthetic metabolites. Either divinyl ether was directly mutagenic or salmonella metabolized the anaesthetic to a mutagen. Many other compounds containing the vinyl moiety are mutagens (McCann et al., 1975) presumably because this group is highly reactive and can be oxidized to an epoxide (Bartsch et al., 1975).

The findings with trichloroethylene show that it is either not, or only weakly, mutagenic. A 30% increase in revertant colonies occurred reproducibly at 1 and 3% vapour concentrations in desiccator assays with strain TA100. Some authors (Chiu et al., 1978) would not regard this as a positive result, believing that at least a 100% increase in the number of revertant colonies is needed before mutagenicity is is established. Waskell (1978), who has also tested trichloroethylene in the salmonella system, concluded that it was not mutagenic. However, the test conditions used were not the same as in the present study. On the other hand, Simmon, Kauhanen and Tardiff (1977), in a study using metabolic activation systems prepared from both mice and rats, concluded that trichloroethylene was a weak mutagen. This conclusion is supported by the high frequency of hepatocellular carcinoma in B6C3F1 mice treated with commercial trichloroethylene (National Cancer Institute, 1976). Unfortunately, the test samples used in the mouse studies were stabilized with carcinogenic epoxides (Henschler et al., 1977) and were given in large quantities into the stomach. Thus the mutagenic and carcinogenic potential of trichloroethylene remains uncertain.

TABLE II. *Mutagenicity tests*: *A = salmonella—Ames test*; *B = sister chromatid exchange*; *C = fibroblast–8-azagnamne*

Agents	Positive	Negative
Halothane	—	A, B, C
Nitrous oxide	—	A, B, C
Chloroform	—	A, B, C
Enflurane	—	A, B, C
Methoxyflurane	—	A, B
Isoflurane	—	A, B
Cyclopropane	—	A, B
Diethyl ether	—	A, B
Trichloroethylene	A?	A, B
Fluroxene	A, B	—
Divinyl ether	A, B	—
Ethylvinyl ether	B	—

Two other mutagenicity test systems have been used recently to test anaesthetics and in general have confirmed the findings of studies in the salmonella–microsome assay (table II). Sturrock (1977) reported negative results for halothane, chloroform, nitrous oxide and enflurane, using the cultured Chinese hamster fibroblast–8-azaguanine system. The effect of anaesthetics on sister chromatid exchange in Chinese hamster ovary cells also has been measured (Stevens et al., 1977). Nitrous oxide, diethyl ether, trichloroethylene, halothane, enflurane, isoflurane, methoxyflurane and chloroform had no effect, whereas divinyl ether, vinyl ethyl ether and fluoroxene gave positive results.



$F_3C{-}CH_2{-}O{-}CH{=}CH_2$

$H_2C{=}CH{-}O{-}CH{=}CH_2$

FIG. 3. Structural formulae of fluroxene and divinyl ether.

The salmonella–microsome assay has proved useful in the detection of carcinogens as mutagens. Approximately 85% of known animal and human carcinogens examined in this system were mutagenic and nearly all mutagens are carcinogenic (Ames, McCann and Yamasaki, 1975). Our results with the salmonella assay have been supported by data from the Chinese hamster fibroblast–8-azaguanine and sister chromatid exchange systems. Based on all the evidence, we conclude that fluroxene and divinyl ether containing the vinyl moiety (fig. 3) are potential carcinogens. These studies also suggest that the modern inhalation anaesthetic agents, nitrous oxide, halothane, enflurane, cyclopropane and methoxyflurane, are not carcinogenic.

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MUTAGENICITE DES ANESTHESIANTS PAR INHALATION: TRICHLOROETHYLENE, ETHER DIVINYLE, PROTOXYDE D'AZOTE ET CYCLOPROPANE

RESUME

On a évalué *in vitro* le potentiel mutagénique du trichloroéthylène, de l'éther divinyle, du protoxyde d'azote et du cyclopropane par essai de conformité microbien à l'aide de deux souches de *Salmonella typhimurium* TA1535 et TA100, dépendant d'histidine. Des agents anesthésiants, en diverses concentrations, ont été mis à incuber avec des bactéries, en présence ou en l'absence d'un système d'enzyme préparé à partir de foie de rat traité aux enzymes inductibles. Le protoxyde d'azote et le cyclopropane n'ont pas été mutagéniques, alors que l'éther divinyle a donné une forte réaction positive. Les résultats obtenus avec le trichloroéthylène ont été équivoques. Ces études, ainsi que les précédentes, effectuées avec le système de salmonella, de même que les études de mutagénicité effectuées à l'aide de différents systèmes d'essais, indiquent que les anesthésiants modernes par inhalation ne sont de toute vraisemblance pas mutagéniques.

DIE MUTATIONSFÄHIGKEIT DER INHALATIONSNARKOSE: TRICHLORÄTHYLEN, DIVINYLÄTHER, LACHGAS UND ZYKLOPROPAN

ZUSAMMENFASSUNG

Es wurde das mutagene Potential von Trichloräthylen, Divinyläther, Lachgas und Zyklopropan *in vitro* mittels Mikrobenanalyse beurteilt, in der zwei histidin-bezogene Stämme von *Salmonella typhimurium*, TA1535 und TA100, verwendet wurden. Narkosemittel in verschiedenen Konzentrationen wurden mit Bakterien in der Gegenwart oder Abwesenheit eines Enzymsystems inkubiert, das von, in Rattenleber herbeigeführten Enzymen hergestellt wurde. Lachgas und Zyklopropan waren nicht mutagen, wohingegen Divinyläther eine stark positive Reaktion ergab. Für Trichloräthylen waren die Ergebnisse zweideutig. Diese und vorangehende Studien mit dem Salmonella-System deuten zusammen mit Mutationsfähigkeitsuntersuchungen, die andere Testsysteme verwenden, darauf hin, dass es unwahrscheinlich ist, dass moderne Inhalationsnarkosemittel mutagen sind.

MUTAGENICIDAD DE ANESTESIAS POR INHALACION: TRICLOROETILENO, ETER DIVINILICO, OXIDO NITROSO Y CICLOPROPANO

SUMARIO

Se evaluó el potencial mutagénico de trocloroetileno, éter divinílico, óxido nitroso y ciclopropano *in vitro* mediante evaluación microbial, empleando dos cepas de *Salmonella typhimurium* dependientes de histidina, TA1535 y TA100. Se incubaron diversas concentraciones de agents anestésicos con bacteria en la presencia o ausencia de un sistema de enzimas preparado con hígado de rata inducido con enzimas. El óxido nitroso y el ciclopropano no fureon mutagénicos, mientras que el éter divinílico dio una respuesta positiva fuerte. Los resultados del tricloroetileno fueron ambiguos. Tanto éstos como los estudios anteriores realizados con el sistema de salmonella, juntamente con estudios de mutagenicidad que se valieron de pruebas diferentes, indican que es poco probable que los agentes anestésicos modernos por inhalación sean mutagénicos.

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REGIONAL BLOOD FLOW IN NORMOVOLAEMIC AND HYPOVOLAEMIC HAEMODILUTION

An experimental study

B. ROSBERG AND K. WULFF

SUMMARY

The effects on the circulation of limited normovolaemic haemodilution with dextran 70 and subsequent haemorrhage to a mean arterial pressure of 60 mm Hg were studied with isotope-labelled microspheres in the dog. Following haemodilution, cardiac output, stroke volume and systemic oxygen transport increased. The distribution of oxygen to the heart, liver (hepatic artery), spleen and carcass (mainly muscle, skeleton and skin) was increased, while a decrease in oxygen supply to the brain was found. Following haemodilution and haemorrhage, cardiac output, systemic oxygen transport and mixed venous oxygen tension decreased. Blood flow was redistributed to maintain the cerebral, renal, hepatic arterial and coronary circulations, mainly at the expense of blood flow to the carcass and through systemic arterio–venous shunts. Thus, limited normovolaemic haemodilution does not affect the normal circulatory response to moderate haemorrhagic hypotension.

Haemodilution is practised widely, particularly in situations where bank blood is not available, for increasing blood flow in low-flow states and, during operation, to reduce the need for transfusion of bank blood. Oxygen supply to tissues is maintained, following haemodilution (Laks et al., 1973; Messmer et al., 1973; Kessler and Messmer, 1975) by an increased cardiac output or by increased oxygen extraction from blood (Carey, 1974), or both. However, increased cardiac output is useful only if oxygen supply to tissues is maintained. Few reports are available on regional blood flow distribution in normovolaemic haemodilution. Race, Dedichsen and Schenk (1967), using flow meters, demonstrated a redistribution of blood flow towards the coronary and vertebral artery systems, and away from the renal, hepatic and carotid arteries. In anaemia, reduction in renal blood flow with no change in flow through the common carotid and femoral arteries was found by Grupp and others (1972). No study demonstrating the effect of haemorrhage on flow distribution in the haemodiluted animal is available.

Using the microsphere technique in studies of regional coronary blood flow, Buckberg and Brazier (1975) showed that the endo–epicardial ratio of flow was unchanged in moderate haemodilution, with a haemoglobin concentration in the range 5–10 g dl^{-1}. In canine hearts, working under load, there was a reduction of the proportion of flow to the subendocardium, which is the part of the heart most vulnerable to ischaemia (Hoffman and Buckberg, 1975).

This investigation was designed to study the distribution of cardiac output in the dog following normovolaemic haemodilution with dextran 70, using the microsphere technique (Rudolph and Heymann, 1967). In addition, the effect of uncompensated haemorrhage was studied.

METHODS

Six mongrel dogs, weighing 16–18 kg (mean 16.7 kg), were used in the experiment, while one dog and three rabbits were used for methodological studies. The animals were deprived of food for 12 h before the experiment.

Four to six days before the experiment a polyethylene catheter was implanted in the left atrium via a thoracostomy, performed under pentobarbitone anaesthesia and controlled ventilation. The catheter was filled with heparin and its distal end was knotted and buried subcutaneously. On the day of the experiment the dogs were anaesthetized with pentobarbitone 25 mg kg^{-1}, and anaesthesia was maintained during the study with additional doses. The trachea was intubated, the dog placed in a supine position and the lungs ventilated artificially at a rate of 13 b.p.m. with a tidal volume adjusted to produce a constant end-tidal carbon dioxide concentration of

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about 5%. The subcutaneous end of the left atrial catheter was retrieved and rinsed with saline. A catheter was placed in the aorta, via the femoral artery, for pressure recordings, to obtain samples for blood-gas analysis and for collecting blood during the haemodilution procedure. A Swan–Ganz catheter was introduced into the pulmonary artery and a catheter was placed in the inferior vena cava for inducing haemorrhagic hypotension. The positions of the catheters were checked by fluoroscopy.

Initial measurements (measurement I) about 1 h after the induction of anaesthesia comprised:

(a) mean arterial and pulmonary arterial pressure recordings using appropriate transducers;
(b) determination of cardiac output, arterial blood-gas analysis and measurement of haematocrit and haemoglobin concentrations;
(c) regional flow measurements by injection of the first dose of microspheres, labelled with strontium-85 through the left atrial catheter.

Haemorrhage of 20 ml kg^{-1} was then effected and this volume was replaced simultaneously with the same volume of dextran 70 (Macrodex 6% in saline, Pharmacia AB, Sweden). Five minutes following haemodilution measurements (a) and (b) were repeated and a second dose of microspheres (labelled with ytterbium-169) was injected (measurement II).

Blood was then withdrawn from the catheter in the inferior vena cava until the mean arterial pressure was approximately 60 mm Hg. Immediately following the bleeding, measurements (a) and (b) were repeated (measurement III). The third dose of microspheres, labelled with cerium-141, was injected. Five minutes following the last measurement, the animals were killed with pentobarbitone, given into the heart.

Arterial and mixed venous blood samples were analysed for pH, Pco_2, Po_2 and oxygen saturation (ABL 1, Radiometer, Denmark) at 37 °C. The blood-gas values were corrected to the dog's rectal temperature.

Haematocrit was measured with heparinized microhaematocrit tubes centrifuged at 8000 rev min^{-1} for 5 min.

Cardiac output was determined by a thermodilution technique (Fegler, 1954), using the Swan–Ganz catheter (model 93–117–7F, Edwards Laboratories, S. Ana, Calif., U.S.A.) with a thermistor in its tip (Forrester et al., 1972; Woods, Scott and Harkin, 1976) and a cardiac output computer (model 9510, Edwards Laboratories). The thermal indicator, 5 ml of 5.5% glucose at a temperature of 0–2 °C, was injected into the superior vena cava. Five determinations, three before and two immediately after injection of the microspheres, were performed during each period of measurement and the mean value was calculated.

Arterial (Ca_{O_2}) *and mixed venous* ($C\bar{v}_{O_2}$) *oxygen content* were calculated as follows:

$$Co_2 = 1.34 \cdot \mathrm{Hb} \cdot So_2 + 0.023 \cdot Po_2$$

where So_2 = percentage saturation of haemoglobin with oxygen; Po_2 = oxygen tension (kPa); 1.34 = oxygen capacity of haemoglobin (millilitre oxygen per gram haemoglobin) and 0.023 = oxygen solubility coefficient (ml kPa^{-1}).

Systemic oxygen transport was expressed as the product of cardiac output and arterial oxygen content (Nunn and Freeman, 1964).

Oxygen consumption, $\dot{V}o_2$ (ml min^{-1}) was calculated from the formula

$$\dot{V}o_2 = (Ca_{O_2} - C\bar{v}_{O_2}) \times \mathrm{CO} \times 10$$

where $(Ca_{O_2} - C\bar{v}_{O_2})$ = arterio–venous oxygen content difference (ml dl^{-1}) and CO = cardiac output (litre min^{-1}).

Calculation of distribution of blood flow. The microspheres (15 ± 5 (SD) μm in diameter) were labelled with the radionuclides strontium-85, ytterbium-169 and cerium-141 respectively (3M Company, St Paul, Minn., U.S.A.) and suspended in dextran 10 ml. Aggregation was prevented with one drop of Tween 20. Depending on the activity of the microspheres, 500 000–1 500 000 spheres were used for each injection.

The technique and measurements of organ blood flow were performed according to the principles of Rudolph and Heymann (1967). Three rabbits and one dog were used initially for assessing the technique. Each rabbit received a single intracardiac injection of one of the radionuclides. The kidneys and liver were removed, frozen and their radioactivity measured in order to determine the interference between the three radionuclides in the chosen gamma-spectrometer channels. The dog, prepared with a catheter in the left atrium, received an injection of all three differently labelled microspheres. The infused activity, measured with the syringe in a specially adapted, water-filled "phantom" (Ericsson, 1971) was compared with sum of the activities for each radionuclide in the measured organs. The activity of ytterbium-169, measured in the "phantom" was underestimated compared with the activity of the organs and the other two radionuclides. Therefore, when calculating the injected dose of ytterbium in the experimental dogs, the measured activity was multiplied by a predetermined correction constant (1.154).

Organ radioactivity was measured (Ericsson, 1971) in pieces weighing not more than 100 g, in a lead-shielded scintillation detector with a 4×3-inch (10×7.6-cm) thallium-activated sodium iodide crystal 38 cm from the centre of the specimen. The output of the detector was connected to a gamma-spectrometer (Canberra scaler, model 818), with window settings 155–235 keV (ytterbium-169), 90–155 keV (cerium-141) and 390–550 keV (strontium-85). Blood flow in the coeliac artery, preportal area, liver and carcass were calculated from the values observed. The sum of values found for the stomach, spleen, hepatic artery, pancreas and duodenum was taken as a measure of the flow through the coeliac artery; the sum of the measurements of the splanchnic organs except the liver (hepatic artery), as the preportal value. The difference between the sum of the activities measured and the activity of the isotope injected was taken as carcass activity.

Measurement of endo–epicardial flow ratio. The canine hearts were first measured as above. In five of the dogs the anterior wall of the left ventricle between the anterior and posterior descending coronary vessels was isolated and cut tangentially into three layers of equal thickness, representing the sub-epicardium, mid-myocardium and sub-endocardium. Each layer was subsequently cut into four to nine smaller pieces, weighed and measured in a two-channel well-type scintillation counter (Nuclear Chicago, Ridle 33–13A) with a crystal size of 2×$1\frac{1}{8}$ inch (5×2.9 cm). The specimens were measured twice, with the window settings at 75–500 keV (^{169}Yb-window), 200–540 keV (^{141}Ce-window) and 450–600 keV (^{85}Sr-window) respectively. The ratio between the sub-endo- and sub-epicardium (endo–epicardial) was then calculated for each radionucleide.

Calculations were made of the mean and standard error of the mean. The significance of the difference between two means was estimated with Student's *t* test for paired observations.

RESULTS

Following haemodilution

Isovolaemic exchange of 20 ml kg^{-1} blood with dextran 70 decreased the haematocrit from 33±1.0 (mean±SEM) to 25±0.6 (mean±SEM). Despite the reduced arterial oxygen contents, systemic oxygen transport increased at measurement II, as a result of an increased cardiac output produced by an increase in stroke volume. Haemodilution did not change the calculated oxygen consumption (table I). However, the oxygen consumption was small in comparison with the findings of most workers. This may be related to the hypothermia present in the experimental animals. The changes in blood flow distribution following haemodilution are shown in table II. The fractional distribution of cardiac output to the carcass and spleen was increased at the expense of the fractions to the brain, kidneys, small bowel and

TABLE I. *Measurements and calculations before (I) and the mean differences after haemodilution (II) and after haemorrhage (III). Compared with measurement I:* $^{*}P<0.05$; $^{**}P<0.01$; $^{***}P<0.001$

	I—Control data		II—After haemodilution		III—After haemorrhage	
	Mean	SEM	Mean difference (II−I)	SEM_{diff}	Mean difference (III−I)	SEM_{diff}
Cardiac output (litre min^{-1})	1.6	0.2	+0.9***	0.2	−0.4*	0.1
Stroke volume (ml min^{-1})	14	1.7	+7***	1.6	−2	1.4
Haematocrit (%)	33	1	−8***	0.6	−10***	1.3
Pa_{O_2} (kPa)	14.1	0.6	+0.3	0.7	−0.6	0.4
Pv_{O_2} (kPa)	7.1	0.3	+0.6	0.4	−2.0**	0.5
Pa_{CO_2} (kPa)	5.0	0.2	+0.2	0.2	−0.1	0.5
MAP (mm Hg)	105	7	+3	3	−46***	9
MPAP (mm Hg)	11	4	0	1	−3	3
Heart rate (beat min^{-1})	112	6	+7	5	−11	7
O_2 transport (ml min^{-1})	204	26	+54*	19	−80**	17
O_2 consumption (ml min^{-1})	36	3.4	+4	1.9	+17*	6.9
Temperature (°C)	35.1	0.3	−0.8**	0.2	−1.5**	0.4

TABLE II. *Fractional distribution of cardiac output and individual organ blood flow before (I) and after (II) haemodilution. Compared with control data (I):* $^{*}P<0.05$; $^{**}P<0.01$; $^{***}P<0.001$

	Before haemodilution (I)				Following haemodilution (II)			
	Fraction (%)		Flow (ml 100 g^{-1} min^{-1})		Fraction (%)		Flow (ml 100 g^{-1} min^{-1})	
Organ	Mean	SEM	Mean	SEM	$Mean_{diff}$ (II−I)	SEM_{diff}	$Mean_{diff}$ (II−I)	SEM_{diff}
Heart	5.4	0.4	71.6	11.0	+0.0	±0.5	+41.6***	±9.0
Lungs	14.8	3.3	328.5	122.1	−0.8	±2.8	+141.9	±93.7
Kidneys	21.6	2.2	639.8	44.1	−0.6*	±1.9	+132.6	±82.7
Hepatic artery	5.2	2.8	10.1	4.0	+0.7	±3.2	+12.8	±6.9
Spleen	3.0	0.5	75.3	19.2	+1.7*	±0.6	+95.8***	±17.7
Stomach	2.4	0.4	25.8	5.9	−0.8	±0.4	+0.9	±4.9
Small bowel	13.1	2.0	46.2	8.7	−3.6*	±1.4	+5.9	±5.3
Colon	3.7	0.5	65.2	10.1	−0.8**	±0.2	+15.4	±7.5
Brain	1.9	0.3	35.2	1.6	−0.8*	±0.3	+0.3	±3.4
Derived values. Total flow (ml min^{-1})								
Preportal	22.2	2.16	368.8	64.5	−3.5	±1.8	+104.8	±42.8
Total splanchnic	27.4	2.19	426.8	42.4	−3.6	±3.4	+173.8*	±68.1
Carcass	28.9	2.6	479.1	77.0	+10.4*	±3.8	+523.7***	±80.9

† Including arterio–venous shunted microspheres from the systemic circulation.

TABLE III. *Distribution of oxygen to individual organs before (I) and the mean differences after haemodilution (II) and after haemorrhage (III). Compared with I:* $^{*}P<0.05$; $^{**}P<0.01$; $^{***}P<0.001$

	I—Control data (ml 100 g^{-1} min^{-1})		II—After haemodilution (ml 100 g^{-1} min^{-1})		III—After haemorrhage (ml 100 g^{-1} min^{-1})	
Organ	Mean	SEM	$Mean_{diff}$ (II−I)	SEM_{diff}	$Mean_{diff}$ (III−I)	SEM_{diff}
Heart	9.1	1.53	+2.3	1.11	−3.3	1.30
Kidneys	79.6	5.67	−1.5	7.59	−24.2*	7.16
Hepatic artery	1.3	0.51	+1.2	0.81	+2.1	1.25
Spleen	8.9	2.57	+8.5*	2.60	−1.2	2.79
Stomach	3.3	0.74	−0.6	0.61	−1.6	0.77
Small bowel	5.9	1.14	−0.6	0.84	−2.9	1.17
Colon	8.3	1.38	−0.1	0.99	−4.1*	1.36
Brain	4.4	0.20	−0.9*	0.29	−0.28	0.43
Derived value. Total oxygen supply (ml min^{-1})						
Carcass	60.8	10.54	+40.1*	10.39	−29.5*	9.94

colon–rectum. No significant changes were noted for the heart, lungs, liver (hepatic artery) and stomach.

Oxygen supply (table III) to the heart, liver (hepatic artery), spleen and carcass was increased, while a decrease in the supply of oxygen to the brain was found. The endo–epicardial ratio of distribution of microspheres at measurement I, 1.46×0.06 (SEM), was not changed significantly by haemodilution, although there were individual variations.

Following haemodilution and bleeding

The reduction of mean arterial pressure to 60 mm Hg (table I) was accomplished by withdrawing 26±1.5 (mean±SEM) ml kg^{-1} of blood (i.e. about 30% of the calculated blood volume in the dog). In comparison with measurements II, there was a decrease in cardiac output ($P<0.001$), stroke volume ($P<0.001$) and heart rate ($0.01>P>0.001$). A decrease in systemic oxygen transport ($P<0.001$)

TABLE IV. *Fractional distribution of cardiac output and individual organ blood flow in the haemodiluted dogs (II) and the mean differences after haemorrhage (III). Compared with II:* $^*P<0.05$; $^{**}P<0.01$; $^{***}P<0.001$

	II—After haemodilution				III—After haemorrhage			
	Fraction (%)		Flow (ml 100 g^{-1} min^{-1})		Fraction (%)		Flow (ml 100 g^{-1} min^{-1})	
Organ	Mean	SEM	Mean	SEM	$Mean_{diff}$ (III – II)	SEM_{diff}	$Mean_{diff}$ (III – II)	SEM_{diff}
Heart	5.4	0.1	113.2	10.7	+0.6	0.6	−54.6***	10.5
Lungs†	14.0	2.6	470.4	99.1	−8.1**	2.2	−371.3**	103.3
Kidneys	15.6	1.1	772.3	105.7	+7.4	3.1	−219.9*	82.0
Hepatic artery	5.9	1.8	24.2	6.8	+9.1*	3.9	+9.3	12.3
Spleen	4.8	0.5	171.1	22.4	−0.3	0.6	−93.7***	18.5
Stomach	1.6	0.2	29.7	6.7	+0.5	0.4	−10.0*	6.1
Small bowel	9.5	0.8	52.1	5.1	+1.8	1.4	−22.6**	5.9
Colon–rectum	2.9	0.3	80.6	8.6	+0.4	0.3	−37.8***	8.1
Brain	1.1	0.1	35.4	3.6	+1.5***	0.3	+4.5	4.0
Derived values. Flow (ml min^{-1})								
Preportal	18.5	0.6	468.2	41.3	+2.6	1.8	−210.7***	30.7
Total splanchnic	23.8	1.9	600.6	54.0	+12.3*	3.9	−149.1*	58.1
Carcass	39.3	2.7	1002.8	168.1	−12.8*	5.6	−686.3***	100.1

† Including arterio–venous shunted microspheres from the systemic circulation.

and an increase in oxygen consumption ($0.05>P>0.01$) produced a reduction in mixed venous oxygen tension ($P<0.001$).

The blood flow distribution following bleeding as compared with the distribution in the haemodiluted dogs is shown in table IV. The fractional distribution of cardiac output to the brain and liver (hepatic artery) was increased significantly at the expense of the fractions to carcass and lungs. There was a reduction in total blood flow to all organs with the exception of the liver and brain.

The endo–epicardial ratio of distribution of microspheres, 1.06 ± 0.16 (SEM), decreased significantly ($P<0.05$) following bleeding.

DISCUSSION

The animals in this study tolerated thoracotomy well and there were no signs of pleural effusion or bleeding at examination after sacrifice. However, the operation may be responsible for the rather low haematocrit value (33 ± 1, mean ± SEM) found at the start of the investigation.

The validity of the microsphere method for measurement of organ blood flow has been demonstrated in fetal sheep and goats, dogs, monkeys and rabbits (Rudolph and Heymann, 1967; Neutze, Wyler and Rudolph, 1968; Kaihara et al., 1969; Hoffbrand and Forsyth, 1971). In this study, the injection of microspheres caused no changes in cardiac output, systemic arterial pressure or heart rate. Pentobarbitone anaesthesia in the dog usually causes tachycardia and reduction in cardiac output, cerebral, splanchnic and renal blood flow (Price, 1960). Using the microsphere technique, Ericsson (1972) demonstrated a decrease in cerebral and an increase in liver fraction of cardiac output following 30 min of anaesthesia. In a previous study of dogs (our own unpublished observations) no significant changes in cardiac output, stroke volume or systemic arterial pressure were noted during 2 h of anaesthesia. This accords with the observations of Priano, Traber and Wilson (1969) who found that prolonged anaesthesia caused minimal haemodynamic changes. All measurements in this study were performed during anaesthesia.

The response to exchange of blood 20 ml kg^{-1} with dextran 70 in this study included increases in cardiac output, stroke volume and systemic oxygen transport. These findings are in agreement with several studies of the immediate reactions to normovolaemic anaemia (Guyton and Richardson, 1961; Messmer et al., 1972; Laks et al., 1973; Restorf et al., 1975).

Following haemodilution the fractional distribution to carcass (mainly muscle, skeleton and skin) increased by 35%. Blood flow fraction to skin was found to increase by 60% following extreme haemodilution (Yoshikawa and Yamamura, 1975). In monkeys with postoperative anaemia the fraction of cardiac output delivered to the skin was also increased significantly (Hoffbrand and Forsyth, 1971).

The blood flow fraction to the lungs is the sum of the flow through the bronchial arteries and systemic arteriovenous shunting. This shunting is known to take place during pentobarbitone anaesthesia in the dog (Kaihara et al., 1968; Ohlsson, 1971).

No significant change was found in the fractional distribution of cardiac output to the liver. This is in accordance with the observations of Yoshikawa and Yamamura (1975).

The fraction of cardiac output distributed to the heart did not change after haemodilution, and thus myocardial blood flow increased by 58%. In studies by Race, Dedichsen and Schenk (1967) and Yoshikawa and Yamamura (1975) myocardial blood flow increased by a proportionally greater amount than the cardiac output. However, these authors studied more severe anaemia, in which the increases in cardiac output were not sufficient to compensate for the reduction in oxygen content. The findings in the present study, in which systemic oxygen transport increased 34%, could be a manifestation of the mechanism described by Allela and colleagues (1955) and Berne (1964), in which coronary blood flow is regulated not so much by cardiac output as by cardiac work.

Haemodilution did not change the endo-epicardial ratio of flow measured with 15-μm microspheres. This is in agreement with the findings of Buckberg and Brazier (1975), using 8–10-μm microspheres. The ratio in this study was 1.46, compared with 1.07 in the study by Buckberg and Brazier (1975). As pointed out by Domenech and colleagues (1969) the ratio obtained with smaller microspheres is closer to that found by diffusible indicators. It may be that there is a tendency to underestimate the epicardial flow with the microspheres used in this study.

The fractional distribution of cardiac output to the kidneys decreased significantly following haemodilution. This has been reported not only in acute dilutional anaemia (Race, Dedichsen and Schenk, 1967; Grupp et al., 1972; Yoshikawa and Yamamura, 1975), but also in moderate chronic anaemia (Hoffbrand and Forsyth, 1971; Vatner, Higgins and Franklin, 1972). There is normally a large arteriovenous oxygen content difference across the renal vascular bed, which should tolerate a reduction of arterial oxygen content without necessarily impairing oxygen delivery (Vatner, Higgins and Franklin, 1972). In this study, the 6% decrease in flow to the kidneys was accompanied by a 3% reduction in renal oxygen supply.

Haemodilution has been shown to increase cerebral blood flow (Michenfelder and Theye, 1969; Paulson et al., 1973). In this study, blood flow to the brain did not change, and the fraction of cardiac output delivered to the brain was reduced. W. Stelter (personal communication), using the microsphere technique (15 μm), also found a decreased fractional distribution to the brain following haemodilution from a haematocrit of 44 to one of 33, while further haemodilution to a haematocrit of 20 increased the cerebral fraction of cardiac output. Anaesthesia should not be responsible for this change, as it has been shown that 6 h of pentobarbitone anaesthesia does not reduce cerebral oxygen consumption or blood flow (Häggendal, Nilsson and Norbäck, 1966). It was shown by these authors that changes of red cell concentration in the haematocrit range 30–60% did not influence cerebral blood flow, which increased at lower haematocrit values, and correlated with a decreased oxygen capacity. In this study, the limited reduction in haematocrit, from 33 to 25%, may have been too small to cause a significant change in cerebral blood flow.

A reduced proportion of flow to the gastrointestinal tract was found. This has been reported in moderate chronic anaemia (Hoffbrand and Forsyth, 1971; Vatner, Higgins and Franklin, 1972), while Race, Dedichsen and Schenk, (1967) noted no change and Yoshikawa and Yamamura (1975) an increased ratio of flow in extreme haemodilution.

The central haemodynamic response to withdrawal of approximately 30% of the calculated blood volume in the dog is in agreement with the reactions described in the non-haemodiluted animal by Ericsson (1971).

The increased oxygen consumption found in this study is probably caused by increased plasma catecholamine concentrations, known to occur during haemorrhage (Chien, 1967; Haddy, Overbeck and Daughterty, 1968).

The fractional distribution of the cardiac output following bleeding indicated differences in local vascular response, with an increased fraction to "vital" organs such as heart, brain and liver, but also to the gastrointestinal tract, at the expense of the carcass fraction. The reduction of the fraction to the lungs suggested that in addition to a reduction in bronchial artery flow, there was closure of arteriovenous shunts. A comparison of the fractional changes of distribution in this study with those obtained from our laboratory (Ericsson, 1972) after withdrawal of 30% of the blood volume in dogs which were not anaemic shows the same pattern. Thus the moderately haemodiluted dog has a normal response to uncompensated blood loss. It consists of an increased oxygen extraction from the blood, and a redistribution of regional blood flow.

The decreased endo-epicardial ratio suggested a diversion of flow within the heart following bleeding. Such a change has been reported to occur in extreme haemodilution (haemoglobin concentration less than 5 g dl^{-1}) and in dogs with aortic stenosis haemodiluted to a haemoglobin concentration in the range 5–10 g dl^{-1} (Buckberg and Brazier, 1975). As shown by Winbury, Howe and Hefner (1969) and Winbury (1971), the sub-endocardium in resting normal dogs has more open capillaries and less arteriolar tone. This is caused by autoregulatory mechanisms elicited by a smaller oxygen tension in sub-endocardial tissue in comparison with epicardial tissue. Dilatation of arterioles following a hypoxic stimulus is, therefore, probably greater in epicardial tissue. This may be the mechanism responsible for the diversion of flow during posthaemorrhagic hypotension seen in this study. Since no control dogs were studied, it is not possible to judge the influence of anaemia on this response. However, it may be presumed that the anaemic dog, with dilated coronary vessels, is more likely to exhibit this mechanism in situations of reduced myocardial oxygen supply or increased oxygen demand, or both.

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DEBIT SANGUIN REGIONAL LORS D'UNE HEMODILUTION NORMOVOLEMIQUE ET HYPOVOLEMIQUE

Etude expérimentale

RESUME

On a étudié sur le chien, les effets qu'ont sur la circulation une hémodilution normovolémique limitée de dextran 70 et l'hémorragie qui lui a fait suite à une pression artérielle moyenne de 60 mm Hg, à l'aide de microsphères marquées par un isotope. Après l'hémodilution, le débit cardiaque, le volume systolique et le transport d'oxygène systémique ont augmenté. La répartition de l'oxygène au cœur, au foie (artère hépatique), à la rate et au reste du corps (surtout aux muscles, au squelette et à la peau) a augmenté, alors qu'on a constaté une diminution de l'alimentation en oxygène du cerveau. Après l'hémodilution et l'hémorragie, le débit cardiaque, le transport d'oxygène systémique et la tension de l'oxygène veineux mélangé ont diminué. Le débit sanguin a été redistribué afin de maintenir les circulations cérébrale, rénale, artérielle hépatique et coronaire, surtout aux dépends du flux sanguin au reste du corps et par l'entremise de shunts systémiques artério-veineux. Ainsi, l'hémodilution normovolémique limitée n'affecte pas la réaction circulatoire normale à une hypotension hémorragique modérée.

DER ÖRTLICHE BLUTSTROM BEI NORMOVOLÄMISCHER UND HYPOVOLÄMISCHER BLUTVERDÜNNUNG

Eine experimentelle Untersuchung

ZUSAMMENFASSUNG

Die Einwirkungen einer begrenzten normovolämischen Blutverdünnung mit Dextran 70 und nachfolgender Blutung zu einem mittleren arteriellen Druck von 60 mm Hg auf den Kreislauf wurden mit, durch Isotope gekennzeichneten Zentrosomen im Hund studiert. Nach der Blutverdünnung erhöhte sich das Herzminutenvolum, das Herzschlagvolum und der systemische Sauerstofftransport. Die Sauerstoffverteilung zum Herzen, der Leber (Leberarterie), der Milz und dem Körper (hauptsächlich Muskeln, Skelett und Haut) war höher, wohingegen ein Abfall in der Sauerstoffversorgung zum Gehirn festgestellt wurde. Nach Blutverdünnung und Blutung nahmen Herzminutenvolum, systemischer Sauerstofftransport und gemischte venöse Sauerstoffspannung ab. Der Blutstrom wurde zur Erhaltung der Gehirn-, Nieren-, Leberarterien- und Herzkreisläufe hauptsächlich auf Kosten des Blutstroms zum Körper und durch systemische arteriovenöse Seitenverbindungen neuverteilt. Eine begrenzte normovolämische Blutverdünnung hat daher keinen Einfluss auf die normale Kreislaufreaktion auf eine mässige hämorrhagische Hypotonie.

CIRCULACION REGIONAL DE SANGRE EN HEMODILUCION NORMOVOLEMICIA E HIPOVOLEMICA

Un estudio experimental

SUMARIO

Se estudiaron los efectos ejercidos sobre la circulación por una limitada hemodilución normovolémica con dextran 70 y la hemorragia subsiguiente, a una presión arterial media de 60 mm Hg mediante microesferas maracadas isotópicamente en el perro. Tras la hemodilución, aumentó el volumen-minuto cardíaco, el volumen de sangre por latido y el transporte de oxígeno a todo el cuerpo. La distribución de oxígeno al corazón, hígado (arteria hepática), bazo y cuerpo (principalmente los músculos, esqueleto y pielo mientras que se descubrió una disminución en el suminist)r, de oxígeno al cerebro. Tras la hemodilución y la hemorragia, disminuyó el volumen-minuto cardíaco, el transporte de oxígeno al cuerpo y la tensión de oxígeno venoso mezclado. La circulación de la sangre fue redistribuida para mantener las circulaciones cerebral, renal, hepática, arterial y coronaria, especialmente a expensas de la circulación de sangre al cuerpo y por medio de derivaciones arteriovenosas sistemáticas. Por lo tanto, la hemodilución normovolémica limitada no afecta la respuesta circulatoria normal a la hipotensión hemorrágica moderada.

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ACUTE AND SUBCHRONIC NEUROMUSCULAR BLOCKING CHARACTERISTICS OF STREPTOMYCIN: A COMPARISON WITH NEOMYCIN*

C. LEE AND A. J. C. DESILVA

SUMMARY

The characteristics of the neuromuscular block produced by streptomycin *in vivo* were studied on the sciatic–tibialis anterior nerve–muscle preparation of eight anaesthetized cats. The lungs of the animals were ventilated mechanically and normocarbia was maintained. During acute exposure to streptomycin (within 2 h), ED_{50} for blockade of the twitch was 56 (SEM ± 5) mg kg^{-1} of the base. The characteristics of block were similar to those of neomycin-induced block in some aspects. There was absence of train-of-four fade and tetanic fade, partial sparing of the responses elicited at 10 Hz and 20 Hz, and total sparing of the 50 Hz tetanus, as well as the post-tetanic twitch. In contrast to neomycin-induced neuromuscular block, however, post-tetanic exhaustion was not observed and prolonged exposure to streptomycin (22–28 h) did not change the characteristics of the block. We conclude that, despite their chemical similarities, streptomycin and neomycin block neuromuscular transmission differently.

The unique characteristics of the neuromuscular block produced by neomycin have been described previously (Lee et al., 1976) and the difference between the block induced, *in vivo*, by the aminoglycoside antibiotics and the polypeptide antibiotics has been stressed (Lee et al., 1976; Lee, Chen and Nagel, 1977). Recently Wright and Collier (1977) reported differences *in vitro* between neomycin and streptomycin, the two most important aminoglycosides with neuromuscular-blocking properties, in their predilection for the prejunctional and the postjunctional structures. Thus, not only dissimilar but also similar antibiotics may block neuromuscular transmission by inherently different mechanisms. The purpose of this present study was to determine whether the characteristics of the neuromuscular block produced by streptomycin differed from those of neomycin *in vivo* also.

METHODS

The methods used by Flacke (1972) and by ourselves (Lee et al., 1976; Lee, Chen and Nagel, 1977) in our previous studies on antibiotics have been combined and modified. Eight healthy cats of 2.0–3.2 kg (mean 2.4 kg; SD 0.4) were anaesthetized with an intraperitoneal injection of alpha-chloralose 60 mg kg^{-1} and pentobarbitone 10 mg kg^{-1}. Tracheotomy was performed and mechanical ventilation was instituted and adjusted to produce normocarbia. The sciatic–tibialis anterior nerve–muscle preparation, which has been described previously (Lee et al., 1976) was used. The sciatic nerve was stimulated at 0.1 Hz (twitch). This was interrupted only for the application of other modes of stimulation as follows: 2 Hz for 2 s (train-of-four), 10 Hz for 2 s, 20 Hz for 2 s (partial tetanization), 50 Hz for 5 s and 100 Hz for 1 s (tetanus). The stimulus was 0.1 ms square electric pulse of supramaximal voltage generated by a Grass S88 stimulator. The presence or absence of tetanic fade was determined by the 50-Hz tetanus. The first post-tetanic twitch was elicited 10 s after the end of the 50-Hz tetanus. Subsequent post-tetanic twitches were followed to determine the time course of facilitation and possible exhaustion. Following the determination of baseline (control) values streptomycin sulphate, dissolved in 0.89% saline, was injected i.v. To determine the dose required, appropriate bolus doses of streptomycin were injected until an almost total block of the twitch was established. Cumulative ED_{50} and ED_{95} were determined. Spontaneous recovery was timed. Following this, a 50% block of the twitch was established repeatedly by additional bolus injections of streptomycin, and the effects on

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the various modes of stimulation observed. After each tetanus, recovery of the twitch from the post-tetanic facilitation was awaited before the response to another mode of stimulation was examined. On completion of these studies, reversal of the block was tested by the injection of edrophonium chloride 0.2 mg kg^{-1} to the cat at a point of 80% block of the twitch. The effect of calcium chloride 10 mg kg^{-1} was examined similarly 1 h later. The cat was rested until the next morning. Overnight, an additional amount of streptomycin sulphate was infused into three cats over a period of 5–8 h to increase the total exposure to the drug. Next morning, the acute experiment was repeated, with the exception that 4-aminopyridine 0.6 mg kg^{-1} was used instead of edrophonium or calcium chloride. For general support, each cat received an infusion of lactated Ringer's solution with 5% dextrose at the rate of 20 ml kg^{-1} during the initial preparation and period of stabilization, 20 ml kg^{-1} during the acute session, 30 ml kg^{-1} overnight, and another 20 ml kg^{-1} during the subchronic session on the 2nd day. For maintenence of anaesthesia, each cat received an additional 70 mg kg^{-1} of alpha-chloralose overnight. Throughout the experiment the body temperature of the cat was maintained within 1 °C of its normal value (37–38.5 °C) by a warming mattress and a heating lamp.

RESULTS

The total amount of streptomycin base (mean ± SEM) given to each cat was 194 ± 18 mg kg^{-1} during the acute session and 142 ± 12 mg kg^{-1} during the 2nd day. Three cats received additional 178 mg kg^{-1}, 246 mg kg^{-1} and 865 mg kg^{-1}, respectively overnight. During the acute session ED$_{50}$ for the twitch was 56 ± 5 mg kg^{-1}, and ED$_{95}$ was 88 ± 8 mg kg^{-1}. The neuromuscular block was of immediate onset, each incremental dose reaching its full effect in 2–3 min. The time to 50% recovery (from 75% block to 25%) was 5.2 ± 0.5 min. Full recovery from 80% block required 15–20 min. On the 2nd day, ED$_{50}$ and ED$_{95}$ were 43 ± 4 mg kg^{-1} and 72 ± 7 mg kg^{-1} of the base, respectively. Both values represented a slight but statistically significant increase in sensitivity following prolonged exposure ($P < 0.02$). The 50% recovery time was 5.9 ± 0.8 min, a value not significantly different from that of the 1st day ($P > 0.2$).

In the presence of a 50% block of the twitch, train-of-four twitches and tetanus did not fade. The post-tetanic twitch was augmented markedly. There was no secondary post-tetanic exhaustion. Muscle responses evoked by the trains of stimuli with a stimulus frequency greater than 0.1 Hz retained more than 50% of their respective controls. The greater the stimulus frequency, the more was the response spared from block (fig. 1). The 50-Hz and the 100-Hz tetanic responses equalled or exceeded their respective controls. The post-tetanic twitch was spared also. Sparing of these responses from block in the presence of a diminished twitch resulted in more than doubling of the tetanus (50 Hz) to twitch and the post- to pre-tetanic twitch ratios during block. These ratios were 10.1 ± 0.8 and 4.3 ± 0.2 respectively during a 50% block, as opposed to 4.3 ± 0.4 and 1.9 ± 0.4 respectively, at control. Following prolonged exposure, there continued to be no train-of-four or tetanic fade. The tetanus to twitch ratio and other indicators of the nature of block remained virtually unchanged (fig. 1).

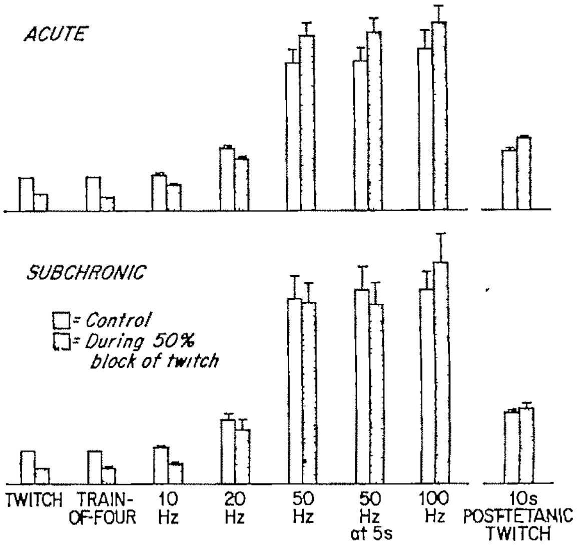

FIG. 1. Characteristics of neuromuscular block during acute and subchronic exposure to streptomycin in the cat. Height of columns represents the relative force of contraction of the twitch or of the tetanus at its peak. "Acute" session was within 1–2 h, "subchronic" after 22–28 h of exposure to streptomycin in doses sufficient to produce neuromuscular blockade. "Train-of-four" refers to the fourth of a train of four twitches evoked at 2 Hz. Note that 10-Hz and 20-Hz responses were relatively spared, while 50-Hz and 100-Hz responses were totally spared, despite 50% block of the single twitch. The fourth twitch of a train-of-four equalled the single or its first twitch and the 50-Hz tetanus maintained its initial force at 5 s, without fade. The characteristics of block remained essentially unchanged after prolonged exposure.

Edrophonium chloride 0.2 mg kg^{-1} and calcium chloride 10 mg kg^{-1}, tested during the 1st day, increased the twitch from 20% of control (80% block) to 69 ± 4% and 70 ± 3% of control, respectively. 4-Aminopyridine 0.6 mg kg^{-1}, tested on the 2nd day, restored the twitch to control within 8 ± 2 min of injection. The reversal was followed by a prolonged overshoot of the twitch response. At its peak, which occurred 71 ± 15 min after the injection of 4-aminopyridine, the twitch response averaged 138 ± 10% of control.

The mean arterial pressure, which was 99 ± 10 mm Hg before the injection of streptomycin, decreased to 87 ± 6 mm Hg 2 min after the injection of the first 30 mg kg^{-1} of streptomycin. The mean arterial pressure, which averaged 93 ± 4 mm Hg immediately before the injection of 4-aminopyridine, increased to 118 ± 8 mm Hg 5 min after administration.

DISCUSSION

The present study revealed the similarities and the dissimilarities between the neuromuscular blocking characteristics of streptomycin and those of neomycin. The similarities were the absence of fasciculation, the absence of train-of-four and tetanic fade, and the sparing of the partial and the full tetanus in the presence of depression of the twitch. These features of the block produced by aminoglycosides were obviously not like those of tubocurarine. The dissimilarities were twofold and were both qualitative. With neomycin-induced neuromuscular block a brief post-tetanic facilitation was followed quickly by exhaustion of the twitch (Lee et al., 1976), whereas this was not shared by streptomycin. Another difference was the absence of the time-dependent changes in the nature of block following prolonged exposure to streptomycin. With neomycin, Flacke (1972) observed an alteration of the block to a "curare-like" pattern after 24 h of subchronic exposure (130–350 mg kg^{-1}).

A study of this type enables proper delineation of each type of neuromuscular block, for its own interest and for the use of such knowledge in the differential diagnosis of clinical problems. It permits the matching and interpretation of the various signs of block observed *in vivo* with the various mechanisms of action observed *in vitro*. *In vitro*, neomycin decreases predominantly the influx of the calcium ion into the motor nerve terminal, which in turn decreases the output of acetylcholine. By comparison, streptomycin is more effective in reducing the muscle motor endplate response to acetylcholine, although it decreases the output of the transmitter (Wright and Collier, 1977). The common features of streptomycin- and neomycin-induced neuromuscular block can be attributed plausibly to their well-known "magnesium-like" anti-release activity (Vital Brazil and Prado-Franceschi, 1969; Pittinger and Adamson, 1972). Both high stimulus frequency and post-tetanic facilitation tend to overcome this type of block (del Castillo and Katz, 1954). The differing features are more difficult to explain. Presumably neomycin has a transmitter-depleting effect. With pre-existing depletion, the post-tetanic state of facilitated release may deplete further the transmitter supply, so that secondary exhaustion follows initial facilitation. The time-dependent and changing nature of neomycin-induced neuromuscular block has been attributed also to its prejunctional effect (Flacke, 1972). With streptomycin, it appears that neither tetanic stimulation nor prolonged exposure results in a depletion of transmitter of comparable magnitude.

In the past those characteristics of neuromuscular blockade which have clinical relevance could be divided into depolarizing and non-depolarizing categories. Recently, we have realized that not all non-depolarizing agents block similarly or cause a fade (Lee, Chen and Katz, 1977); neither do all antibiotics, all aminoglycosides or all prejunctional blockers (personal observations) block with similar characteristics. In the future, improved techniques of examination may reduce further the gap between the diversity of knowledge of the mechanism of action of various neuromuscular blocking drugs and what can be demonstrated *in vivo*. For example, we have observed that, while alpha-bungarotoxin neuromuscular block (post-junctional) has no effect on the refractoriness of neuromuscular transmission, beta-bungarotoxin (pre-junctional) reduced it markedly. In this respect, polymyxin B behaves like alpha-bungarotoxin. Streptomycin behaves like beta-bungarotoxin. Neomycin resembles beta-bungarotoxin except that the post-tetanic facilitation reduces the refractoriness while the secondary post-tetanic exhaustion enhances the effect further. We feel that this observation might help to confirm the pre- or post-junctional mechanism of action of these neuromuscular blocking antibiotics *in vivo* and eventually provide a method of differential diagnosis which would have clinical applicability.

In conclusion, streptomycin-induced neuromuscular block in the cat is characterized by the absence of fade and a selective sparing of the tetanus and the post-tetanic twitch. In these respects, it is similar to the block produced by neomycin, another aminoglycoside antibiotic. However, during block the post-tetanic facilitation was not followed by a secondary post-tetanic exhaustion and there were no time-dependent changes in the characteristics of the block following prolonged exposure. Based on these qualitative differences, we conclude that even antibiotics of similar chemical structure may block neuromuscular transmission differently. Prejunctional effects appear to play a less important role in a block induced by streptomycin as compared with neomycin.

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CARACTERISTIQUES DU BLOCAGE NEUROMUSCULAIRE AIGU ET SOUS-CHRONIQUE PAR LA STERPTOMYCINE: COMPARAISON AVEC LA NEOMYCINE

RESUME

Les caractéristiques du blocage neuromusculaire produit par la streptomycine *in vivo* ont été étudiées sur une préparation de nerf–muscle sciatique–tibial antérieur de huit chats anesthésiés. Les poumons des animaux étaient ventilés par des moyens mécaniques et la normocarbie a été maintenue. Pendant l'exposition aigue à la streptomycine (et en l'espace de 2 h) l'ED_{50} pour le blocage de la crispation a été de 56 mg kg^{-1} de la base (erreur type des moyennes ±5). Les caractéristiques du blocage ont été similaires sous certains aspects à celles d'un blocage provoqué par la néomycine. Il y a eu une absence d'atténuation de la série de quatre crispations et d'atténuation tétanique, une modération partielle des réactions découvertes à 10 Hz et à 20 Hz et une modération totale du tétanos à 50 Hz de même que de la crispation post-tétanique. Par contraste au blocage neuromusculaire provoqué par la néomycine, l'épuisement post-tétanique n'a cependant pas été observé et l'exposition prolongée à la streptomycine (22 à 28 h) n'a pas modifié les caractéristiques du blocage. Nous en concluons qu'en dépit de leurs similarités chimiques, la streptomycine et la néomycine bloquent la transmission neuromusculaire de manières différentes.

AKUTE UND SUBCHRONISCHE NEUROMUSKULÄRE BLOCKIERUNGSCHARAKTERISTIKEN VON STREPTOMYZIN: EIN VERGLEICH MIT NEOMYZIN

ZUSAMMENFASSUNG

Die Charakteristiken des durch Streptomyzin *in vivo* hervorgerufenen neuromuskularen Blocks wurden an der Präparation der vorderen Hüftbein/Schienenbein-Nerven/Muskeln von acht narkotisierten Katzen studiert. Die Lungen der Tiere wurden mechanisch ventiliert und im Blut wurde ein normaler Kohlensaurespiegel aufrechterhalten. Während der akuten Einwirkung von Streptomyzin (innerhalb von 2 Stunden) war die mittlere wirksame Dosis fur eine Blockade der Zuckung 56 (SEM, Standardabweichung ±5) mg kg^{-1} der Grunddosis. In mancher Hinsicht waren die Blockmerkmale ähnlich denen eines durch Neomyzin induzierten Blocks. Es gab keinen Schwund in der Viererfolge und tetanischen Schwund, in den bei 10 Hz und 20 Hz hervorgelockten Reaktionen gab es teilweise Verschonung und Vollverschonung bei dem 50-Hz-Tetanus und den posttetanischen Zuckungen. Im Gegensatz zu dem durch Neomyzin induzierten neuromuskulären Block wurde jedoch keine posttetanische Erschöpfung beobachtet und eine langere Einwirkung von Streptomyzin (22–28 Stunden) veränderte nichts an den Charakteristiken des Blocks. Wir schliessen daraus, dass Streptomyzin und Neomyzin trotz ihrer chemischen Ähnlichkeit die neuromuskuläre Übertragung auf verschiedene Art blockieren.

CARACTERISTICAS DE BLOQUEO NEUROMUSCULAR AGUDO Y SUBCRONICO DE ESTREPTOMICINA: COMPARACION CON NEOMICINA

SUMARIO

Se estudiaron las características del bloqueo neuromuscular producido por estreptomicina *in vivo* en una preparación de nervio–músculo ciático–tibial anterior de ocho gatos anestesiados. Los pulmones de los animales se ventilaron mecánicamente y se mantuvo normocarbia. Durante la exposición aguda a la estreptomicina (dentro de 2 h), el ED_{50} para el bloqueo de sacudida muscular fue de 56 (SEM ±5) mg kg^{-1} de la base. Las características del bloqueo fueron semejantes en ciertos aspectos al bloqueo inducido por neomicina. Hubo ausencia de debilitamiento de "serie de cuatro" y debilitamiento tetánico, conservación parcial de las reacciones producidas a 10 Hz y 20 Hz, y conservación total del tétanos de 50 Hz, además de la sacudida post-tetánica. Sin embargo, en contraste con el bloqueo neuromuscular inducido por neomicina, no se observó agotamiento post-tetánico y la prolongada exposición a estreptomicina (22–28 h) no cambió las características del bloqueo. Concluímos que, a pesar de su semejanza química, la estreptomicina y la neomicina bloquean la transmisión neuromuscular de forma diferente.

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EFFECTS OF AGEING ON THE PHARMACOKINETICS OF PANCURONIUM

K. McLeod, C. J. Hull and M. J. Watson

SUMMARY

The effects of age on the pharmacokinetics of pancuronium were investigated. The distribution volume of pancuronium did not appear to be age-dependent, but elimination of the drug decreased with increasing age. The clinical implications of these findings are discussed.

In several pharmacokinetic studies of pancuronium bromide, it was noted that there was considerable parametric variation between healthy subjects (McLeod, Watson and Rawlins, 1976; Agoston et al., 1977; d'Hollander, Camu and Sanders, 1978; Hull et al., 1978). This paper considers the possibility that some of this variation was a result of the effects of ageing.

METHODS

Nineteen adult patients (11 male, eight female) undergoing general anaesthesia for a variety of non-urgent surgical procedures were investigated. Their ages ranged between 20 and 86 yr (mean 57 yr). No patient showed any evidence of renal failure or of any other major systemic disease. In each patient, anaesthesia was induced with thiopentone sodium, and maintained with nitrous oxide in oxygen and increments of fentanyl. The patient was given a single dose of pancuronium bromide 4 mg i.v., the trachea was intubated and mechanical ventilation was instituted. Serial samples of venous blood were collected as described previously (McLeod, Watson and Rawlins, 1976) and the plasma concentrations of pancuronium were estimated by a modification (Watson and McLeod, 1977) of the spectrofluorimetric method described by Kersten, Meijer and Agoston (1973).

An optimal biexponential curve of the general form $C = A.e^{-\alpha t} + B.e^{-\beta t}$ was fitted to the serial plasma concentrations for each patient, and the parameters of the corresponding two-compartment model determined using an analog method (Hull and McLeod, 1976). In each patient, drug clearance ($\dot{V}$), the apparent volume of distribution (V_β) and the steady-state distribution volume (V_{ss}) were calculated (appendix). The results were compared with the ages and weights of the patients, using correlation and linear regression analysis.

RESULTS

In concordance with previous studies (McLeod, Watson and Rawlins, 1976; Hull et al., 1978) it was found that, in all patients, the decays in the plasma concentrations were fitted by biexponential curves and, therefore, could be represented by two-compartment open models (table I). V_β, V_{ss} and $\dot{V}$ were

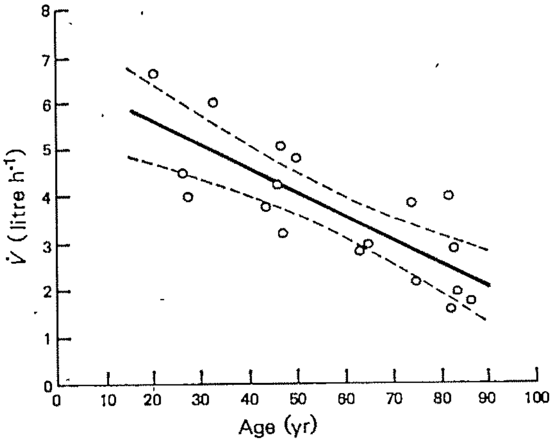

FIG. 1. Pancuronium clearance ($\dot{V}$) plotted against age, with a least-squares linear regression line, and 95% confidence limits for the regression estimate.

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TABLE I. *Details of patients and measurements*

Patient	Age (yr)	Weight (kg)	$\dot{V}$ (litre h^{-1})	V_β (litre)	V_{SS} (litre)	Plasma urea (mmol litre^{-1})
1	82	52.0	1.54	11.67	12.8	7.3
2	84	53.0	1.93	7.47	10.0	5.8
3	55	62.3	3.80	10.86	14.2	6.0
4	26	71.0	4.51	9.89	16.0	5.5
5	74	55.5	3.82	13.18	15.5	7.3
6	75	74.0	2.19	7.87	15.3	5.2
7	82	55.0	3.99	13.01	17.2	4.3
8	86	58.0	1.74	10.22	11.4	4.7
9	83	45.0	2.88	9.09	11.8	6.4
10	65	61.5	2.93	7.97	11.3	5.3
11	63	66.2	2.83	8.33	11.4	5.3
12	33	53.6	6.00	12.07	15.1	5.4
13	27	71.0	3.40	8.65	11.7	5.4
14	50	82.0	4.80	10.91	13.9	5.0
15	47	64.0	3.17	7.83	11.4	4.6
16	47	77.0	5.06	12.52	18.8	4.5
17	46	87.0	4.28	8.84	11.9	3.5
18	20	73.6	6.64	14.76	17.4	6.5
19	44	70.0	3.81	9.32	14.0	6.2

calculated for each model (appendix), and correlated with the age and weight of the patient.

Correlation and regression analysis

$\dot{V}$: age (fig. 1)
$r = -0.794$ ($P < 0.001$)
$y = 6.56 - 0.05x$

$\dot{V}$: weight
$r = 0.12$ ($P > 0.1$)

V_β : age
$r = 0.29$ ($P > 0.1$)

V_β : weight (fig. 2)
$r = 0.11$ ($P > 0.1$)

V_{SS} : age
$r = 0.33$ ($P > 0.1$)

V_{SS} : weight
$r = 0.21$ ($P > 0.1$)

Of the six correlations, that between age and clearance was highly significant, but none of the other correlation coefficients (r) differed significantly from zero.

To test the possibility that both weight *and* age contributed to the variation in the clearance and distribution volumes, three-way linear regressions were computed for each variable. An examination of residuals showed that in no instance was the variance about the regression reduced significantly by the introduction of the third term, so the hypothesis was rejected, and our conclusions are based on the original two-variable analysis.

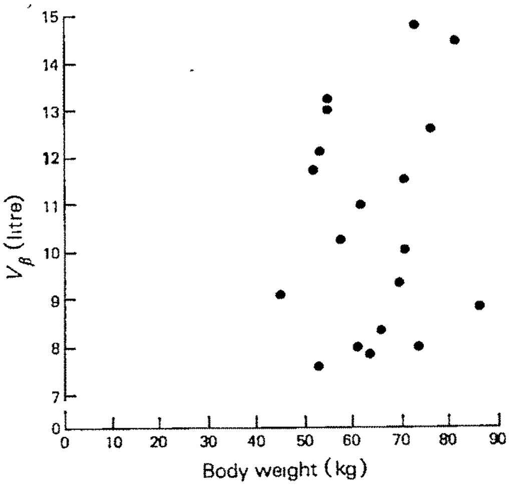

FIG. 2. Apparent distribution volume V_β plotted against patient weight. There is no significant correlation.

DISCUSSION

Our findings suggest that the only significant relationship between ageing and the pharmacokinetics of pancuronium was a progressive reduction in the rate of elimination.

Since pancuronium is excreted by both hepatic and renal routes, a diminution of either or both could be responsible for the changes observed. Approximately 50% of injected pancuronium is excreted unchanged in the urine, with only 10% conjugated and excreted by the liver (Agoston et al., 1973). As renal function has been observed to diminish with advancing age (Davies and Shock, 1950; Rowe et al., 1976), it is probable that the decrease noted in the clearance of pancuronium was related to changes in renal function. However, it has been noted also that the ability of the liver to metabolize certain drugs, for example propranolol (Castleden, Kaye and Parsons, 1975), diminished with age, so that a degree of hepatic involvement in the changes observed in the clearance of pancuronium cannot be discounted.

Neither the apparent nor the steady-state distribution volumes correlated significantly with either age or weight, even when considering both age and weight simultaneously in a multiple-correlation analysis. This does not, of course, mean that no such relationships exist, since correlation analysis may be unreliable in small samples of large populations. However, it must be said that this study does not support the popularly held concepts that:

(a) elderly patients have reduced distribution volumes, and *therefore* require smaller doses of drug to achieve the desired effect;

(b) pancuronium should be given to adults on a "dose per kg" basis, in the belief that distribution volume increases with body weight.

Our findings contrast with those of Chan and others (1975), who found reductions in both the distribution volume and the clearance of pethidine in elderly subjects.

There are, of course, other factors not considered by this study, which could influence the clinical effect of pancuronium when given to older patients. Changing patterns of plasma protein binding (Hayes, Langman and Short, 1975), redistribution of cardiac output, changes in receptor sensitivity or margin of safety could all modify the clinical response (Hull et al., 1978). Our results suggest that, as patients age, the rate of decline of the plasma concentration after a single i.v. dose will decrease, so that an increase in recovery time would be expected.

The predictive value of this study is summarized in figure 3. The regression line from figure 1 is re-plotted, with the 95% confidence limits for an estimate of clearance from a single value of age (one patient). (The validity of the confidence interval is based on the finding that the residuals about the regression in figure 1 do not differ significantly from normality.) It is apparent that at any age within the range 20–90 yr, the clearance can be predicted to an accuracy of approx. ±3.5 litre h^{-1}. Whilst this degree of variation precludes the accurate prediction of plasma clearance in any single patient, the *average* relationship between age and clearance can be defined within much closer limits (fig. 1), so that it can be stated confidently that patients in the 3rd decade of life clear pancuronium twice as fast as those in the 9th decade.

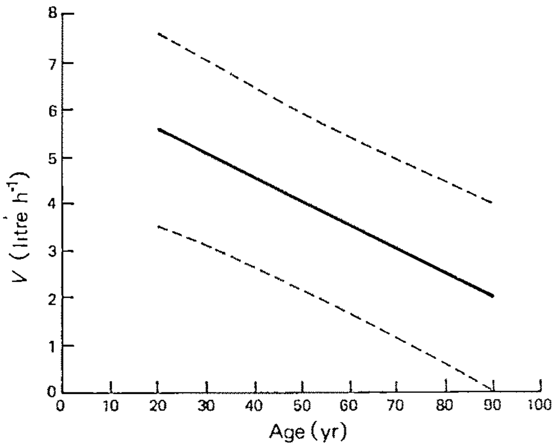

FIG. 3. Prediction of pancuronium clearance (V) from patient age. The regression line is taken from figure 1, and the outer lines are the ±95% confidence limits for a future *single* estimate of V from age.

APPENDIX

Definition of terms

α, β, A, B	Exponents and constants determining the characteristics of a biexponential function (Hull and McLeod, 1976).
V_1 (litre)	Volume of the central compartment of a two-compartment open model. Drug is assumed to enter and leave the model exclusively from this compartment.
V_2 (litre)	Volume of the peripheral compartment of the model.
k_{12} (h^{-1})	Rate constant determining the movement of drug from compartment 1 to compartment 2.
k_{21} (h^{-1})	Rate constant determining the movement of drug from compartment 2 to compartment 1.
k_{10} (h^{-1})	Elimination rate constant.
V_β (litre)	The apparent volume of distribution, calculated from the expression: $V_\beta = (V_1 . k_{10})/\beta$ This parameter relates the amount of drug in the body to the plasma concentration at any time during the post-distributive phase (Gibaldi and Perrier, 1975).

V_{ss} (litre)	The steady-state volume of distribution, calculated from the expression $$V_{ss} = V_1 \cdot [(k_{21}+k_{12})/k_{21}]$$ (Klotz, 1976). It is simply the sum of V_1 and V_2 (Riggs, 1963). Unlike V_β, V_{ss} is independent of the elimination rate constant k_{10} and is a better index of total distribution volume.
$\dot{V}$ (litre h^{-1})	Clearance from the whole model during the post-distributive phase, calculated from the expression: $\dot{V} = V_1 \times k_{10}$.

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EFFETS DU VIEILLISSEMENT SUR LA PHARMACOCINETIQUE DU PANCURONIUM

RESUME

On a fait des recherches sur les effets de l'âge sur la pharmacocinétique du pancuronium. Le volume de diffusion du pancuronium n'a pas semblé dépendre de l'âge, mais l'élimination du médicament a diminué au fur et à mesure qu'augmentait l'âge. On commente dans cet article les implications cliniques de ces observations.

DIE WIRKUNG DES ALTERNS AUF DIE PHARMAKOKINETIK VON PANCURONIUM

ZUSAMMENFASSUNG

Es wurden die Wirkungen des Alters auf die Pharmakokinetik von Pancuronium untersucht. Das Verteilungsvolumen von Pancuronium schien nicht altersabhängig zu sein, aber die Ausscheidung des Mittels nahm mit zunehmenden Alter ab. Besprochen wird die klinische Bedeutung dieses Befundes.

EFECTOS DE AÑEJAMIENTO SOBRE LA FARMACOCINETICA DE PANCURONIO

SUMARIO

Se investigaron los efectos ejercisdo por el añejamiento sobre la farmacocinética de pancuronio. El volumen de distribución del pancuronio no pareció depender de la edad, pero la eliminación de la droga disminuyó al aumentar la edad. Se discuten las implicaciones clínicas de estos descubrimientos.

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COMPARISON OF THE ACTIONS OF DIAZEPAM AND LORAZEPAM

J. W. DUNDEE, W. A. W. MCGOWAN, J. K. LILBURN, A. C. MCKAY AND
J. E. HEGARTY

SUMMARY

Diazepam and lorazepam differ in potency and in the time-course of their action. As a sedative, diazepam 10 mg is equivalent to lorazepam 2–2.5 mg. Diazepam is better absorbed after oral than after i.m. administrations but this does not apply to lorazepam. The clinical effect and amnesia begin more rapidly with diazepam, but last longer following lorazepam. Lorazepam is more effective than diazepam in blocking the emergence sequelae from ketamine. Lorazepam i.v. is followed by a lesser frequency of venous thrombosis.

Diazepam is widely used in anaesthetic practice as a premedicant and sedative–amnesic. In addition, it has been investigated as an induction agent although it is not used commonly for this purpose. Many new benzodiazepines have been studied, but apart from lorazepam most of these differ only slightly from diazepam and these differences relate only to their potency. There are minimal differences in duration of action.

This paper compares some facets of the actions of diazepam and lorazepam in anaesthetic practice. In some instances it summarizes data which have been published elsewhere and it includes new findings. The objective was to give an overall comparison of the two drugs.

Intravenous use

Diazepam has been used for the induction of anaesthesia (Dundee and Wyant, 1976). The onset of action takes 60–90 s, the response is variable and the effect is often too prolonged to be clinically acceptable. Full anaesthesia may require a dose in the range 1–1.5 mg kg^{-1}. Dundee and others (1977) noted a delay of up to 40 min before the peak effect of lorazepam 4 mg and this would make it completely unacceptable for induction of anaesthesia.

We studied the rate of onset of sedation of the two drugs, using the "mean efficacy" score described by Dundee, Moore and Nicholl (1962). A score of 1 (unacceptable) to 5 (ideal) was allocated to the patient's condition based on the degree of drowsiness and absence of apprehension. Groups of approximately 10 patients were given diazepam 10 or 20 mg or lorazepam 4 mg as i.v. preanaesthetic medication. Observations were made at 2, 5, 10, 15, 20 and 30 min after administration. With this method of assessment the peak sedative action of diazepam was reached within 5 min of injection, whereas that of lorazepam was still increasing at 30 min (fig. 1). The sedative effect of diazepam had started to diminish by 10 min, in contrast with the increasing effect of lorazepam at that time.

Figure 1 shows some of the problems of comparing the potency of two drugs with differing time-effect profiles. At 10 min a similar degree of sedation is produced by diazepam 10 mg and lorazepam 4 mg, while at 20 min the average effects of diazepam

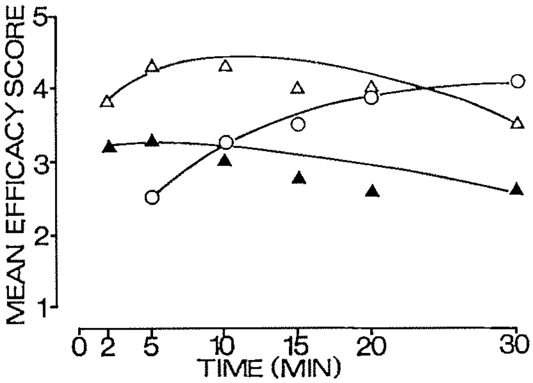

FIG. 1. Mean efficacy score following i.v. injection of diazepam 10 mg = ▲, diazepam 20 mg = △, and lorazepam 4 mg = ○.

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20 mg are similar to those of lorazepam 4 mg. However, the study shows that, in appropriate doses and allowing for the delay in onset of action, i.v. lorazepam is as good as diazepam as a sedative.

Thrombosis, with or without phlebitis, is a common complication of the injection of benzodiazepines. Hegarty and Dundee (1977) have reported a detailed 3–4 and 7–10-day follow-up of the frequency of venous sequelae following diazepam 10 mg and lorazepam 4 mg. Their findings (table I) show the superiority of lorazepam in this respect. The lorazepam was injected in the form available at that time (4 mg ml^{-1}) and not diluted to half this strength, as is now recommended by the manufacturers.

TABLE I. *Frequency of venous sequelae (phlebitis, thrombosis or thrombophlebitis) after diazepam and lorazepam (from Hegarty and Dundee,* 1977)

Drug	Dose (mg)	No. of patients	Total venous sequelae (%) 2–3 days	7–10 days
Diazepam	10	44	23	39
Lorazepam	4	40	8	15

Preanaesthetic medication

Oral diazepam is now a popular premedicant, the usual adult dose being 10 mg. Dundee and others (1977) demonstrated the efficacy of lorazepam for this purpose, the optimum oral dose being 4 mg for adults. This study has been extended to include additional cases with the commercially available 2.5-mg tablet and the findings have been compared with diazepam in patients who are comparable with respect to average age and weight (table II). Again, the methodology was that described by Dundee, Moore and Nicholl (1962), which was used in previous studies of benzodiazepines (Assaf, Dundee and Gamble, 1975). This consists of an evaluation of the degree of drowsiness and apprehension at 20, 40, 60 and 90 min after administration, and a note of side-effects at these times. The doses of lorazepam studied were determined by the commercially available ampoules (4 mg) and tablets (1 and 2.5 mg) except for the 4-mg tablet which was prepared specially for the previous study.

TABLE II. *Details of the patients in the premedicant study*

Drug (mg)	Route	*n*	Mean wt (kg) (±SEM)	Mean age (yr) (±SEM)
Lorazepam 2.5	Oral	100	59.4±0.8	32.8±0.9
Lorazepam 3.5	Oral	20	58.7±2.1	31.8±2.5
Lorazepam 4.0	Oral	100	61.0±1.1	32.0±1.0
Diazepam 10	Oral	50	60.2±1.5	32.9±1.3
Lorazepam 2.0	I.m.	30	60.5±2.2	35.3±2.4
Lorazepam 4.0	I.m.	100	60.0±1.0	30.7±1.1
Diazepam 10	I.m.	100	59.7±1.0	32.9±1.2

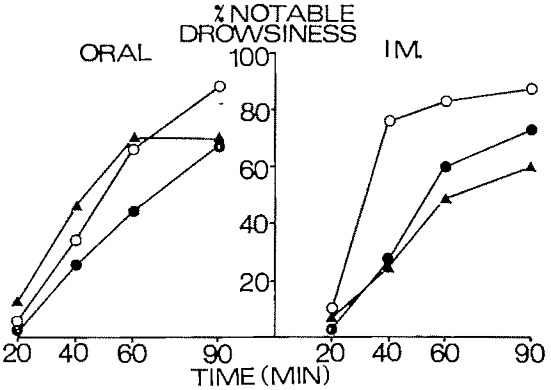

FIG. 2. Percentage of notable drowsiness (good and fair degrees) after diazepam 10 mg = ▲, lorazepam 4 mg = ○ lorazepam 2.5 mg oral or 2.0 mg i.m. = ●.

Figure 2 shows that, in contrast to diazepam 10 mg, the onset of drowsiness with lorazepam 4 mg is more rapid following the i.m. compared with the oral administration. It also shows the expected dose–response effect of lorazepam. There was a slightly more rapid onset of action of oral (but not i.m.) diazepam compared with lorazepam. Although it is difficult to equate the potency of two drugs with different onsets of action, figure 2 would suggest that diazepam 10 mg is approximately equipotent with lorazepam 2–2.5 mg as a sedative–tranquillizer.

Table III shows the results with the commercially available 3.5-mg (1- and 2.5-mg) tablets of lorazepam and the specially prepared 4-mg tablets. The effects of 3.5 mg were almost identical with those of 4 mg. At 60 min significantly more patients had notable

TABLE III. *Percentage frequency of notable drowsiness (good and fair) with three oral doses of lorazepam*

Dose of lorazepam (mg)	Time after administration (min) 40	60	90
2.5	25	44	67
3.5	40	65	85
4.0	34	66	88

drowsiness after 3.5 mg than after 2.5 mg ($\chi^2 = 3.96$; $P < 0.05$), but this difference was less marked at 90 min ($\chi^2 = 2.57$; $P < 0.20$).

In the doses used both diazepam and lorazepam were free from major side-effects and there was no hypotension, marked tachycardia or respiratory depression. However, lorazepam i.m. produced significantly more persistent pain at the site of injection than diazepam (table IV), but this had passed completely by 40 min with both drugs. Again, it should be pointed out that the injected lorazepam was more concentrated than that now currently recommended. Restlessness was also more frequent with i.m. lorazepam, and this persisted for 1 h. This was not a result of persistent injection-site pain as both occurred in only eight patients. Restlessness was not a problem with any oral dose of lorazepam.

TABLE IV. *Comparison of the percentage frequency of some side-effects of i.m. diazepam and lorazepam*

	Pain at site of injection	Restlessness		
	20 min	20 min	40 min	60 min
Lorazepam 4 mg	24	34	26	19
Diazepam 10 mg	12	13	5	7
χ^2	4.88	12.6	16.84	6.37
P	<0.05	<0.0005	<0.0005	<0.025

Ketamine sequelae

I.v. administration of diazepam near the end of operation minimized the unpleasant sequelae from ketamine (Erbguth, Reiman and Klein, 1972; Coppel, Bovill and Dundee, 1973; Kothary and Zsigmond, 1975). However, premedication with diazepam only provided a limited degree of protection in patients undergoing minor surgery, but lorazepam in adequate doses was effective in this respect (Lilburn et al., 1978). Dundee and Lilburn (1978) found a small frequency of emergence delirium and unpleasant dreams after operation in patients undergoing minor gynaecological operations under ketamine anaesthesia and premedicated with lorazepam 4 mg orally or i.m. but the published study did not include the commercially available tablet (2.5 and 3.5 mg). The effect of these has been studied in 75 women anaesthetized with intermittent ketamine (initial dose 2 mg kg^{-1}) for minor gynaecological operations, using the same routine as the study by Lilburn and others (1978). The frequency of severe prolonged (10 min +) delirium and unpleasant dreams (as recalled 6 h later) is given in table V, which also shows the number of patients who would object to having the same anaesthetic on a subsequent occasion. Table V shows the efficacy of lorazepam 4 mg given i.v. This made ketamine very acceptable to patients as an induction agent. The same dose is effective when given by mouth, but the number of patients who would not like the same anaesthetic on a subsequent occasion was unacceptably high with the 2.5-mg tablet as premedication. However, it would appear that the findings with 3.5 mg (1- and 2.5-mg tablets) make this an acceptable premedication for ketamine anaesthesia and superior in this respect to an equivalent dose of diazepam.

Amnesia

The i.v. administration of most benzodiazepines affected the patient's ability to remember objects shown or events occurring for a short period after injection. The duration and intensity of this varied with dose and individual drugs. Figure 3 summarizes our findings with i.v. diazepam and lorazepam. This is based on the subject's ability to recall objects shown at varying times after administration. Amnesia

TABLE V. *Percentage frequencies of sequelae following ketamine 2 mg kg^{-1} after various premedicants, and the patient's opinion of the anaesthetic*

Premedicant	Route	n	Severe emergence delerium	Unpleasant dreams	Anaesthesia unacceptable to patient
Saline	I.v.	50	32	38	64
Diazepam 15 mg	I.v.	20	45	20	30
Lorazepam 4 mg	I.v.	50	0	3	0
Lorazepam 4 mg	Oral	50	0	20	4
Lorazepam 3.5 mg	Oral	20	0	15	10
Lorazepam 2.5 mg	Oral	55	2	34	44

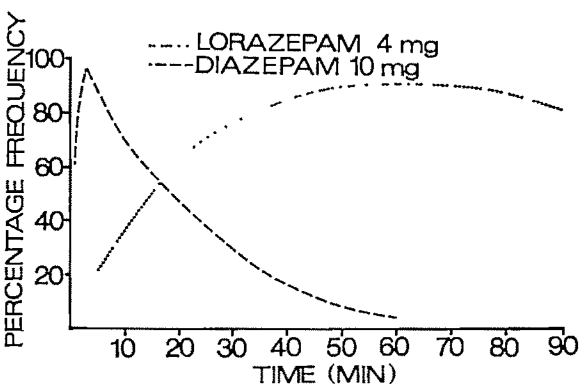

FIG. 3. Percentage frequency of loss of ability to recall objects shown at various intervals following i.v. administration of lorazepam 4 mg and diazepam 10 mg (George and Dundee, 1977).

occurred quickly after diazepam, with recovery by 30 min, by which time the amnesic action of lorazepam was becoming marked (George and Dundee, 1977).

The i.m. injection of diazepam 10 mg caused an insignificant degree of amnesia, but this was enhanced by the addition of hyoscine or opiates. The amnesic action of i.m. lorazepam has not been studied.

Since many patients take both diazepam and lorazepam orally as tranquillizers during the day, it was felt necessary to study their amnesic action following oral administration. Diazepam 10 or 20 mg or lorazepam 2 or 4 mg were given before operation to patients who were shown 10 cards over the next 90 min. Their ability to recognize these was tested 6 h later. Significant failure to identify a card was only found (with either drug) when the patient was notably drowsy at the time of presentation; in this respect there is a difference between the effects of oral and i.v. administration of both drugs. Figure 4 shows the percentage frequency of failure to identify objects after approximately equivalent sedative doses of diazepam and lorazepam. This shows the slower onset of action of lorazepam. Not included in this figure is that lorazepam 1 mg did not appear to affect the memory. However, it should be noted that, in our studies, a 10-mg tablet of diazepam did cause more impairment of memory than an inert tablet (McKay, Dundee and George, 1978).

Plasma concentrations

These have been reported for clinical doses of both diazepam (Gamble, McKay and Dundee, 1973; Gamble, 1975; Gamble, Dundee and Assaf, 1975) and lorazepam (Dundee et al., 1978) following i.m. injection to the thigh.

The rate of uptake of the two drugs is similar and the slower onset of clinical effect of lorazepam cannot be explained on these grounds. A second peak in plasma concentration has been found 6–8 h after oral administration with both drugs, and clinically this may lead to a second period of drowsiness. Whereas the plasma concentrations increase sooner after diazepam 10 mg orally compared with i.m.

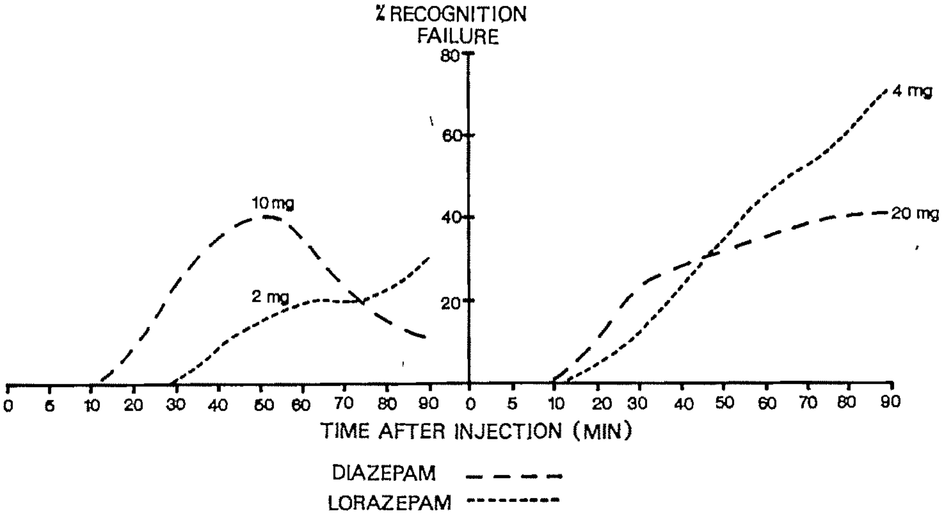

FIG. 4. Percentage frequency of loss of ability to recall objects shown at various intervals following oral administration of two doses of diazepam and lorazepam.

TABLE VI. *Plasma concentrations* ($ng\ ml^{-1}$) *following the oral administration of diazepam* 10 *mg* (*D*) *and lorazepam* 4 *mg* (*L*) *with or without previous i.v. injection of metoclopramide* 10 mg (*M*). (*Mean values* ± *SEM*)

		Time after administration (min)			
	n	15	30	45	60
D	15	65±22.3	122±18.2		205±22.9
D+M	10	218±53.6	240±27.7	233±21.9	211±22.8
L	20	12.6±7.9	22.55±10.41	39.85±16.22	49.00±15.99
L+M	8	12.8±18.32	17.38±14.58	28.00±21.25	39.00±12.60

injection, this relationship was not found with lorazepam—in fact there was a slight delay in the increase of plasma concentrations after the oral administration of the drug.

Gamble and others (1976) found that the i.v. injection of metoclopramide 10 mg hastened the uptake of diazepam from the gastrointestinal tract. The average plasma concentration was significantly greater at 15 ($P<0.05$) and 30 ($P<0.005$) min when metoclopramide had been given compared with a control series (table VI). A similar study with lorazepam 4 mg showed no significant difference in average plasma concentrations with or without metoclopramide. No explanation can be offered for this.

Gamble, Dundee and Gray (1976) also studied plasma concentrations in patients receiving diazepam 5 mg and 10 mg at 4-h intervals for periods of 6–22 days. There was an accumulation of both diazepam and its metabolite for about 8 days, by which time the plasma diazepam concentration reached a plateau while the major metabolite (n-desmethyl diazepam) continued to increase during the period of administration.

A similar study was carried out in seven patients who received lorazepam 4 mg every 4 h for periods of 2–15 days. There was a small accumulation in plasma concentration (measured at the same time after injection) for about 8 days, again followed by a plateau. A typical finding (fig. 5) shows a plateau effect with rapid decrease in plasma concentration on discontinuing the drug with its disappearance from the blood over the next 6 days. In this respect

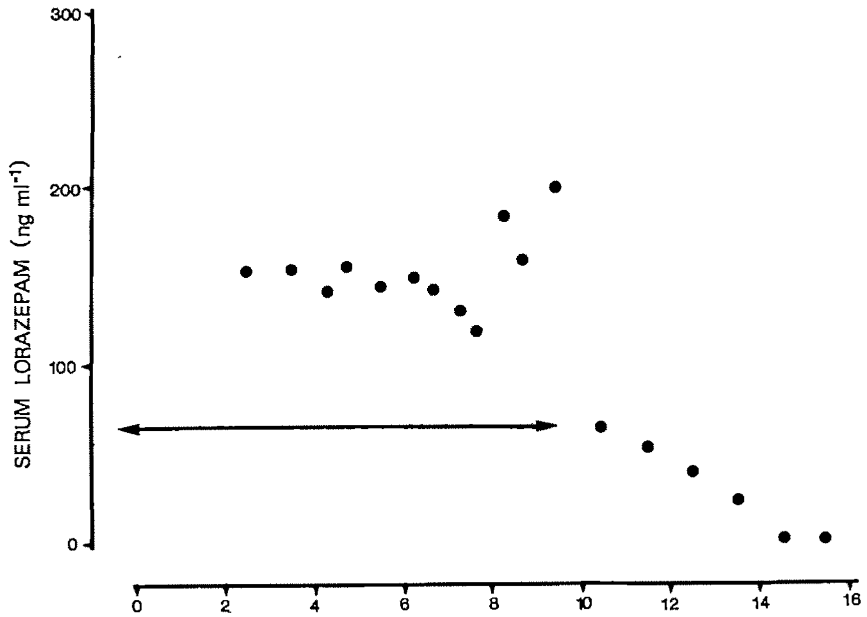

FIG. 5. Typical plasma concentrations in a male (47 yr, 84 kg) during prolonged administration of lorazepam 4 mg at 4-h intervals for 8 days (↔).

diazepam and lorazepam behave very similarly. No metabolite of lorazepam was detected in this study.

In our premedicant studies, it was often possible to estimate plasma concentrations for up to 2 days after administration. By 4–6 h the plasma concentrations were similar irrespective of whether the drugs were given orally or i.v., and this applied to both diazepam and lorazepam. In view of the prolonged soporific effects of the benzodiazepines, the plasma concentrations were estimated at 24 and 48 h after administration of diazepam 10 mg or lorazepam 4 mg in patients who received no medication after operation. The average findings in a small number of patients show the persistence of an appreciable amount of both drugs in the plasma for 48 h (table VII). These values represent 35–40% of peak plasma concentrations still present at 24 h and 25–30% at 48 h. Lorazepam was eliminated from plasma slightly more slowly than was diazepam but the difference was not statistically significant.

TABLE VII. *Plasma concentrations* ($ng\ ml^{-1}$) *of diazepam and lorazepam at 24 and 48 h after oral administration. (Mean values ± SEM)*

	n	24 h	48 h
Lorazepam 2.5 mg	13	17.40 ± 1.7	10.3 ± 2.6
Diazepam 10 mg	10	90.30 ± 10.8	67.9 ± 8.9

DISCUSSION

There is no published detailed comparison of the actions of diazepam and lorazepam with which to compare this study. However, reports on various facets of these drugs (Galloon, Gale and Lancee, 1977) are in agreement with the present findings.

Our results show that diazepam and lorazepam differ quantitatively, rather than qualitatively in their actions and they indicate certain respects in which there is a preference for one or other drug.

Both drugs cannot be recommended as injectable premedicants because of local irritation. By mouth, diazepam requires more precise timing than lorazepam. The latter is particularly useful for "later cases" on an operating list where a delay of a few hours will not result in recovery from sedation. However, the prolonged effect of lorazepam may be a disadvantage for minor operations when rapid recovery is desirable. It has proved particularly useful as a reliable sedative in doses of 2.5–3.5 mg for the night before operation and can be recommended for this purpose. One may hesitate to use lorazepam on both the night before and the morning of operation, and diazepam can be substituted in the latter occasion.

Without discussing the indications for the use of benzodiazepines for induction of anaesthesia, it is obvious that lorazepam is unsuitable for this purpose. However, it can produce a useful degree of sedation and can be used in conjunction with regional analgesia techniques, provided the anaesthetist appreciates the slow onset of action. For outpatient dental procedures, diazepam is preferred.

Amnesia may be regarded as either desirable or undesirable. It is important to appreciate the consistency of amnesia with both drugs and particularly the prolonged amnesia which follows lorazepam. If a short period of amnesia is desired, for example in childbirth or for performance of a nerve block, diazepam is preferred. Diazepam accumulates in the fetus (Gamble et al., 1977) in contrast with lorazepam, following which a maternal/fetal ratio greater than unity has been found (unpublished observations). We have found lorazepam 2–3 mg to be very effective when given i.v. early in labour and there appears to be no deleterious effects on the fetus.

The persistence of such high concentrations of both drugs in the plasma for up to 48 h was unexpected. It shows the need for caution in outpatients and the danger of drug interactions in the period soon after operation.

We have summarized the important differences between diazepam and lorazepam below. These are intended as a guide in deciding which drug is preferable in differing clinical situations.

1. As a premedicant, diazepam 10 mg produces a degree of sedation comparable with 2.0–2.5 mg lorazepam.
2. The duration of action of lorazepam is three to four times greater than that of equivalent doses of diazepam.
3. Oral diazepam produces earlier effects than the equivalent dose given i.m., but this does not apply to lorazepam.
4. These effects occur in parallel with plasma concentrations of the drugs.
5. There is a slow excretion of both drugs from the body and plasma concentrations remain increased for 24–48 h.
6. The main metabolite of diazepam, n-desmethyl diazepam, has an appreciable hypnotic action and accumulates following repeated administrations. This does not apply to lorazepam.

(7) With both drugs there may be a second "peak" concentration 5–8 h after administration.
(8) In equivalent i.v. doses both drugs commonly produce anterograde amnesia which is not wholly dependent on sedation.
(9) Premedication with lorazepam will consistently reduce the undesirable emergence effect of ketamine, while diazepam is unreliable in this respect.
(10) In contrast, the i.v. injection of diazepam near the end of a ketamine anaesthetic will reduce emergence sequelae, but lorazepam is not suitable for this purpose.

ACKNOWLEDGEMENTS

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COMPARAISON DES ACTIONS DU DIAZEPAM ET DU LORAZEPAM

RESUME

Le diazépam et le lorazépam diffèrent du point de vue efficacité et durée d'action. En tant que sédatif, le diazépam à raison de 10 mg équivaut à 2–2,5 mg de lorazépam. Le diazépam est mieux absorbé après administration par voie orale que par voie intramusculaire, mais cela n'est pas applicable au lorazépam. L'effet clinique et l'amnésie commencent plus rapidement avec le diazépam, mais durent plus longtemps avec le lorazépam. Le lorazépam est plus efficace que le diazépam pour bloquer les séquelles provenant de la kétamine. Le lorazepam administré par voie intraveineuse est suivi d'une plus faible fréquence de thrombose veineuse.

VERGLEICH DER WIRKUNGEN VON DIAZEPAM UND LORAZEPAM

ZUSAMMENFASSUNG

Diazepam und Lorazepam unterscheiden sich voneinander in ihrer Wirksamkeit und im Zeitverlauf ihrer Wirkung. Als Beruhigungsmittel sind 10 mg Diazepam 2–2,5 mg Lorazepam ebenbürtig. Diazepam wird besser nach mündlicher als nach intramuskulärar Verabreichung aufgenommen, aber das trifft nicht auf Lorazepam zu. Die klinische Wirkung und Amnesie beginnen schneller mit Diazepam, aber halten nach Lorazepam länger an. Lorazepam ist wirkungsvoller als Diazepam in der Blockierung der Folgeerscheinungen von Ketamin bei Emergenz. Intravenoses Lorazepam bringt weniger häufig eine Thrombophlebitis mit sich.

COMPARACION ENTRE LAS ACCIONES DE DIAZEPAM Y LORAZEPAM

SUMARIO

Diazepam y lorazepam difieren en potencia y en el transcurso de tiempo de su acción. Como sedante, 10 mg de diazepam equivale a 2–2,5 mg de lorazepam. El diazepam es mejor absorbido por administración oral que intramusclar, aunque no es así con el lorazepam. El efecto clínico y la amnesia comienzan más rápidamente con diazepam, pero duran más tras lorazepam. El lorazepam es más efectivo que el diazepam en el bloqueo de la secuela que se presenta al emerger de los efectos de ketamina. El lorazepam intravenoso es seguido por una menor frecuencia de trombosis venose.

Br. J. Anaesth. (1979), 51, 447

PREVENTION OF SUXAMETHONIUM-INDUCED CHANGES IN SERUM POTASSIUM CONCENTRATION BY HEXAFLUORENIUM

Is their combined use justified?

P. A. RADNAY, R. P. BADOLA, A. DALSANIA, E. I. EL-GAWEET AND D. DUNCALF

SUMMARY

Sixty patients, none of whom was suffering from renal failure, received neurolept anaesthesia. They were divided into six groups of 10 patients each. Groups I and IV, II and V, and III and VI were given suxamethonium 0.2, 0.6 and 1.0 mg kg^{-1} respectively. Groups IV–VI were pretreated with hexafluorenium 0.3 mg kg^{-1}. The serum potassium concentration decreased significantly after the induction of anaesthesia and also following the administration of hexafluorenium. Neither suxamethonium 0.2 mg nor 0.6 mg kg^{-1} with or without hexafluorenium restored the potassium concentration to the control value. Suxamethonium 1.0 mg kg^{-1} alone caused the serum potassium to increase to values greater than control; hexafluorenium attenuated this effect. The combination of hexafluorenium and suxamethonium may be of benefit in patients who are anephric or are in chronic renal failure.

While many authors find neurolept anaesthesia using droperidol and fentanyl suitable for patients in chronic renal failure (Trudnowski et al., 1971; Morgan and Lumley, 1975), the choice of neuromuscular blocking agent remains controversial.

Gallamine frequently (Churchill-Davidson, Way and deJong, 1967; Abrams and Hornbein, 1975), pancuronium bromide and tubocurarine occasionally (Logan, Howie and Crawford, 1974; Abrams and Hornbein, 1975) have caused prolonged neuromuscular blockade, which has necessitated ventilatory support following surgery. Suxamethonium, when given rapidly i.v., is known to increase both the degree of fasciculation and the serum potassium concentration (Powell, 1970) and, when administered as a continuous infusion, the total dose may be high, leading to a phase II block (Foldes, 1966a).

The combination of hexafluorenium (Mylaxen) and suxamethonium decreases the amount of suxamethonium required (Foldes, 1960, 1966b; Figueroa, 1968; Campbell and Swerdlow, 1969; Cullen, 1971; Kleine and Moesker, 1976). This study was to determine if this combination would attenuate the effect of suxamethonium on the serum potassium concentration. Hexafluorenium causes histamine release (Selvin and Howland, 1959; Mostert and Kundig, 1964) and bronchospasm has been associated with its use. Fellini, Berstein and Zauder (1963) and Eustace (1967) described bronchospasm following suxamethonium also.

MATERIALS AND METHODS

Sixty patients (18–64 yr) who were not suffering from chronic renal failure and who were undergoing a variety of surgical procedures were studied. They were divided into six groups of 10 patients each.

All received diphenhydramine 75–100 mg, and pethidine 50–75 mg with atropine 0.4–0.6 mg i.m., 90 and 60 min respectively before the start of the study. The oropharynx was sprayed with 1% amethocaine HCl solution to facilitate the insertion of an oropharyngeal airway. Droperidol 150 $\mu g\ kg^{-1}$ and fentanyl 1 $\mu g\ kg^{-1}$ were given over 60 s, followed in 6 min by the inhalation of 75% nitrous oxide in oxygen. Increments of fentanyl 0.5 $\mu g\ kg^{-1}$ were given as required.

The patients in groups I, II and III received suxamethonium 0.2, 0.6 and 1.0 mg kg^{-1} i.v., respectively, injected over 30 s. Those in groups IV, V and VI were given hexafluorenium 0.3 mg kg^{-1} i.v. followed after 5 min by suxamethonium in doses corresponding to groups I, II and III.

Fasciculations were classified as severe, moderate, mild and none. Heart rate, systolic and diastolic arterial pressures were recorded and the e.c.g. was observed.

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Venous blood samples were taken from the arm which was not used for the infusion before and at the completion of the induction of anaesthesia and 1, 3, 5, 10 and 15 min after the completion of the injection of the suxamethonium in all groups; in a pilot study we had found that the change in the serum potassium concentration was maximal between 10 and 15 min. In groups IV–VI the serum potassium concentration was determined also 5 min after the administration of hexafluorenium. The serum potassium concentration was measured using an Orion Biochemical Sodium-Potassium Analyzer (Model SS-30).

Venous pH and $P\text{CO}_2$ were measured before the induction of anaesthesia and 15 min after the administration of suxamethonium.

RESULTS

The characteristics of the patients are presented in table I.

TABLE I. *Age, sex and weight distribution and physical status (ASA classification) of the 60 patients*

Age (yr)		Sex		Weight (kg)		Physcial status	
Mean	Range	M	F	Mean ± SEM	Range	I	II
40.4	18–64	25	35	69.0 ± 1.8	44–110	43	17

No severe fasciculations were observed; the number of moderate fasciculations increased with increasing doses of suxamethonium. The patients who received hexafluorenium did not exhibit fasciculations (table II).

There were no significant changes in either arterial pressure or heart rate (table III) and no arrhythmia was noted in any patient.

TABLE II. *Fasciculations following the administration of suxamethonium i.v.*

Group	Severe	Moderate	Mild	None
I	—	1	8	1
II	—	6	4	—
III	—	9	1	—
IV	—	—	—	10
V	—	—	—	10
VI	—	—	—	10

TABLE III. *Haemodynamic changes (mean ± SEM) during the induction of neuroleptanaesthesia in 30 patients who received hexafluorenium*

	Arterial pressure (mm Hg)		Heart rate (beat min^{-1})
	Systolic	Diastolic	
Before induction	127.3 ± 4.7	73.5 ± 2.0	80.6 ± 2.4
5 min after hexafluorenium	131.8 ± 4.0	76.8 ± 2.0	80.0 ± 2.3

Although we did not measure blood histamine concentration, we did not observe any signs or symptoms of histamine release, such as wealing along the course of the vein or bronchospasm.

The venous pH and $P\text{CO}_2$ values obtained 15 min after the administration of suxamethonium were not significantly different from the values noted before induction.

The serum potassium concentratons at various times throughout the study are detailed in table IV. Following the induction of anaesthesia a decrease in the serum potassium concentration was observed in each group. The mean (± SEM) serum potassium concentration (n = 60) following the induction of

TABLE IV. *Serum potassium concentrations (mmol litre^{-1}) throughout the study (mean ± SEM)*

		Suxamethonium (mg kg^{-1})			Hexafluorenium 0.3 mg kg^{-1} followed in 5 min by suxamethonium (mg kg^{-1})		
		0.2	0.6	1.0	0.2	0.6	1.0
Control		4.07 ± 0.19	4.07 ± 0.09	3.86 ± 0.17	3.72 ± 0.35	4.15 ± 0.28	4.02 ± 0.21
After induction		3.74 ± 0.14	3.69 ± 0.10	3.51 ± 0.12	3.35 ± 0.15	3.67 ± 0.28	3.71 ± 0.20
5 min after hexafluorenium		—	—	—	3.35 ± 0.16	3.53 ± 0.26	3.50 ± 0.16
After i.v. injection of suxamethonium (min)	1	3.53 ± 0.10	3.89 ± 0.07	3.92 ± 0.19	3.45 ± 0.19	3.56 ± 0.23	3.65 ± 0.16
	3	3.46 ± 0.07	3.94 ± 0.14	3.98 ± 0.12	3.40 ± 0.17	3.67 ± 0.21	3.72 ± 0.16
	5	3.56 ± 0.10	3.94 ± 0.12	4.00 ± 0.12	3.44 ± 0.16	3.73 ± 0.22	3.82 ± 0.17
	10	3.50 ± 0.06	3.81 ± 0.09	3.97 ± 0.11	3.46 ± 0.17	3.81 ± 0.24	3.72 ± 0.17
	15	3.58 ± 0.08	3.77 ± 0.09	3.86 ± 0.11	3.57 ± 0.13	3.98 ± 0.30	3.80 ± 0.16

anaesthesia (3.60 mmol litre^{-1} ± 0.07) was significantly less ($P < 0.001$) than the mean value before induction (3.98 mmol litre^{-1} ± 0.07). In the patients in groups V and VI there were futher decreases in serum potassium concentration 5 min after the administration of hexafluorenium 0.3 mg kg^{-1}.

Following the administration of suxamethonium the serum potassium concentration was noted to decrease further in group I, to increase to less than the control in group II and to exceed the control in group III. In the patients who received the combination of hexafluorenium and suxamethonium the changes in the serum potassium concentration were less marked. In group IV the results were similar to those obtained in group I. The serum potassium concentration increased in groups V and VI, but in neither group did it reach the control value during the first 15 min after administration of suxamethonium.

DISCUSSION

Stoelting and Peterson (1975) observed that suxamethonium 1–2 mg kg^{-1} preceded by tubocurarine 0.4 mg kg^{-1} caused changes in the serum potassium concentration, slowing of the heart and junctional rhythm. The latter was also observed by Duncalf and others (1965) with the use of hexafluorenium 0.4 mg kg^{-1}. Those who have shown that hexafluorenium can cause bronchospasm used larger doses and different agents (Selvin and Howland, 1959; Mostert and Kundig 1964) and anxiety about the histamine releasing effect of larger doses of suxamethonium (Fellini, Berstein and Zauser, 1963; Eustace, 1967; Bele-Binda and Valeri, 1971) was not confirmed in our study.

No arrhythmias occured in this series, in contrast to observations by Duncalf and others (1965) and Stoelting and Peterson (1975). Droperidol may have played a role in their prevention (Schotz and Geigler, 1967; Goodman and Gilman, 1975), while diphenhydramine as part of the premedication may have helped to prevent the release of histamine.

Several authors have reported significant, but transient decreases in serum potassium concentration after the administration of halothane, thiopentone, methohexitone, ketamine and diazepam (List, 1967; Logan, Howie and Crawford, 1974; Ball, Dundee and Assaf, 1973; Konchigeri and Tay, 1975). We observed a substantial decrease after induction with neuroleptic agents. This decrease in serum potassium concentration was augmented in many of the patients given hexafluorenium 0.3 mg kg^{-1}. However, the reduction in the serum potassium concentration was not transient, for it persisted through the entire period of observation in groups I and IV (i.e. patients who received suxamethonium 0.2 mg kg^{-1}). In all the patients who received hexafluorenium the serum potassium concentration remained less than the control values during the period of observation. Since acidosis and alkalosis did not occur it is unlikely that these played a role in the changes in potassium concentration (Wong et al., 1973). The cause of the sustained decrease in serum potassium concentration is not clear.

The addition of hexafluorenium prevents the rapid hydrolysis of suxamethonium, thus both the intensity and duration of its block are increased markedly (Foldes, 1960). However, the neuromuscular blockade produced by the combination wears off within a reasonable time without the use of an antagonist and its duration may be adjusted by altering the hexafluorenium–suxamethonium ratio.

We recommend 0.2-mg kg^{-1} increments of suxamethonium. As soon as the interval between two doses of suxamethonium decreases to 10–15 min, we repeat the hexafluorenium in a 0.1–0.15 mg kg^{-1} dose and follow it in 2 min by suxamethonium 0.2 mg. With proper management the patient should breathe spontaneously at the end of surgery. It is rarely necessary to assist the respiration for short periods, as the total amount of suxamethonium used during surgery is small (Foldes, 1966), making this method safe even in patients with abnormal cholinesterase activity. The mixture will eliminate the undesirable side-effects of suxamethonium such as fasciculation, increased intraocular pressure (Dillon et al., 1957) and the increases in serum potassium concentration.

The technique might be safe for anephric patients and for those in chronic renal failure.

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PREVENTION DES VARIATIONS PROVOQUEES PAR LE SUXAMETHONIUM SUR LA CONCENTRATION DE POTASSIUM DANS LE SERUM APRES ADMINISTRATION D'HEXAFLUORENIUM

Leur usage conjoint est-il justifie?

RESUME

Soixante patients, dont aucun ne souffrait d'insuffisance rénale, ont été soumis à une neuroleptanesthésie. On les a divisé en six groupes de 10 patients: Groupes I et IV, II et V, et II et VI auxquels on a administré respectivement du suxaméthonium à raison de 0,2, 0,6 et 1,0 mg kg^{-1}. Les Groupes IV et VI ont été prétraités à l'héxafluorénium sur la base de 0,3 mg kg^{-1}. La concentration de potassium dans le sérum a diminué d'une manière significative après l'induction de l'anesthésie et également après l'administration d'héxafluorénium. Ni le suxaméthonium à 0,2 mg kg^{-1}, ni ce même produit mais à 0,6 mg kg^{-1}, avec ou sans héxafluorénium, n'ont pu ramener la concentration de potassium à la valeur témoin. Le suxaméthonium seul à raison de 1 mg kg^{-1} a fait augmenter le potassium du sérum à une valeur supérieure à la valeur témoin. L'héxafluorénium a atténué cet effet. La combinaison d'héxafluorénium et de suxaméthonium peut être bénéfique pour les malades qui souffrent d'anéphrite ou d'insuffisance rénale chronique.

VERHÜTUNG VON DURCH SUXAMETHONIUM INDUZIERTEN VERÄNDERUNGEN IN DER SERUM-KALIUMKONZENTRATION DURCH HEXAFLOORENIUM

Ist ihre gemeinsame Anwendung gerechtfertigt?

ZUSAMMENFASSUNG

Sechzig Patienten, von denen keiner an einem Versagen der Nieren litt, erhielten neuroleptische Narkose. Sie wurden in sechs Gruppen von je 10 Patienten aufgeteilt. Den Gruppen I und IV, II und V, und II and VI wurden 0,2, 0,6 bzw. 1,0 mg kg^{-1} Suxamethonium gegeben. Gruppen IV–VI wurden mit 0,3 mg kg^{-1} Hexafloorenium vorbehandelt. Die Serum-Kaliumkonzentration nahm nach Narkoseinduktion und auch der Verabreichung von Hexafloorenium bedeutend ab. Weder 0,2 mg noch 0,6 mg kg^{-1} Suxamethonium mit oder ohne Hexafloorenium brachten die Kaliumkonzentration auf den Kontrollwert zurück. Allein 1,0 mg kg^{-1} Suxamethonium verursachte eine Zunahme im Serum-Kalium auf Werte, die über den Kontrollwerten lagen; Hexafloorenium schwachte diese Wirkung ab. Die Hexafloorenium-Suxamethonium-Kombination kann bei solchen Patienten von Nutzen sein, die anephrisch sind oder an chronischem Nierenversagen leiden.

PREVENCION DE CAMBIOS INDUCIDOS POR SUXAMETONIO EN LA CONCENTRACION DE POTASIO EN EL SUERO MEDIANTE HEXAFLUORENIO

¿ Se justifica su empleo combinado ?

SUMARIO

Sesenta pacientes, ninguno de los cuales sufría de deficiencia de los riñones, recibieron anestesia neuroléptica. Se dividieron en seis grupos de diez pacientes cada uno. Los Grupos I y IV, II y V, y III y VI recibieron 0,2, 0,6 y 1,0 mg kg^{-1} de suxametonio, respectivamente. Los Grupos IV a VI fueron pretratados con 0,3 mg kg^{-1} de hexafluorenio. La concentración de potasio en el suero disminuyó significativamente después de la inducción de anestesia y también siguiendo la administración de hexafluorenio. Ni 0,2 mg kg^{-1} ni 0,6 mg kg^{-1} de suxametonio con o sin hexafluorenio pudieron recobrar la concentración de potasio al valor de control; 1,0 mg kg^{-1} de suxametonio solo hizo que el potasio en el suero aumentara a valores superiores a los de control—el hexafluorenio atenuó este efecto. La combinación de hexafluorenio y suxametonio puede ser beneficiosa en pacientes anéfricos o que sufren de deficiencia crónica de los riñones.

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MORBIDITY OF DAY-CASE GYNAECOLOGICAL SURGERY

A comparison of thiopentone and Althesin

R. M. TOWEY, B. J. STANFORD, R. M. BALLARD AND J. R. GILBERT

SUMMARY

To compare two anaesthetic techniques, morbidity following day-case gynaecological surgery in 170 patients was assessed by means of a questionnaire at the time of leaving hospital. A further questionnaire sought information for the evening of the operation, and the 1st and 2nd days after operation. Ninety-four per cent of patients returned the latter questionnaire. There was a high frequency of morbidity extending into the 2nd day after operation. An anaesthetic technique using Althesin and nitrous oxide in oxygen offered no advantage over a technique with thiopentone and nitrous oxide in oxygen and halothane.

Anaesthesia for day-case surgery presents a special problem in that the patient should be well enough to leave hospital within a few hours of the operation. The cost per operation is less for outpatient than for inpatient surgery (Russell et al., 1977), and increasing demands on hospital beds make it likely that the use of day-case surgery will increase.

The present study was performed to investigate postoperative morbidity in day-case gynaecological surgery and to compare two separate anaesthetic techniques: induction with Althesin followed by nitrous oxide in oxygen and intermittent Althesin, and induction with thiopentone and maintenance with nitrous oxide in oxygen and halothane.

METHOD

One hundred and seventy patients (age 15–63 yr; mean 36 yr) undergoing gynaecological procedures (dilatation and curettage, diathermy to the cervix or to vulval warts) were studied. The patients were allocated in equal numbers to the two anaesthetic groups.

Anaesthetic technique

There was no premedication. The anaesthetics were given by senior registrar or consultant anaesthetists, the majority by the authors. In one group anaesthesia was induced with Althesin and maintained with 70% nitrous oxide in oxygen, with further increments of Althesin as necessary. In this group an indwelling needle was used for supplementary injections. In the second group anaesthesia was induced with thiopentone and maintained with halothane vaporized in 70% nitrous oxide in oxygen. The duration of each procedure (induction to end of surgery) was noted.

Recovery

Recovery time was measured as the interval between the end of the operation and the patient's response to her name by opening the eyes.

Postoperative assessment

When each patient was ready to leave hospital, she was given a questionnaire and asked to record the presence or absence of: drowsiness; dizziness; headache; nausea; soreness of the throat, mouth or lips; pain at the injection site; abdominal pain; backache; and muscle pain. A note was made if the patient had vomited on recovery from anaesthesia.

On the 2nd day after operation each patient was asked to complete a second form and return it to the hospital by post. This asked about symptoms listed above at each of the following times: the evening of the day of operation; the 1st day after operation; the 2nd day after operation. For each time the patient was asked to note her ability to perform normal activities and to state if she would have preferred surgery as an inpatient.

RESULTS

One hundred and sixty patients (94%) returned the questionnaire, 80 from each anaesthetic group. The

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TABLE I. *Postoperative morbidity in two groups of 80 patients each. A = intermittent Althesin, nitrous oxide in oxygen anaesthesia; H = thiopentone and halothane in nitrous oxide in oxygen anaesthesia*

	In hospital		At home		Day 1		Day 2	
	A Total (%)	H Total (%)	A Total (%)	H Total (%)	A Total (%)	H Total (%)	A Total (%)	H Total (%)
Drowsiness	39 (49)	33 (41)	44 (55)	46 (58)	24 (30)	26 (33)	8 (10)	17 (21)
Dizziness	24 (30)	33 (41)	25 (31)	28 (35)	13 (16)	17 (21)	10 (13)	9 (11)
Headache	22 (26)	23 (29)	32 (40)	25 (31)	19 (24)	18 (23)	9 (11)	12 (15)
Nausea	16 (20)	16 (20)	23 (29)	20 (25)	9 (11)	13 (16)	8 (10)	5 (6)
Vomiting	4 (5)	8 (10)	5 (6)	3 (4)	1 (1)	0 (0)	0 (0)	0 (0)
Sore throat	2 (3)	4 (5)	3 (4)	6 (8)	2 (3)	5 (6)	2 (3)	3 (4)
Sore mouth or lips	6 (8)	3 (4)	7 (9)	6 (8)	4 (5)	6 (8)	4 (5)	6 (8)
Pain at injection site	8 (10)	3 (4)	13 (16)	3 (4)	8 (10)	1 (1)	6 (8)	0 (0)
Slight abdominal pain	42 (53)	39 (49)	42 (53)	47 (59)	37 (46)	34 (43)	30 (38)	30 (38)
Severe abdominal pain	8 (10)	5 (6)	6 (8)	5 (6)	5 (6)	9 (11)	3 (4)	6 (8)
Backache	28 (35)	17 (21)	32 (40)	31 (39)	34 (43)	32(40)	25 (31)	27 (34)
Muscle ache and pain	7 (9)	8 (10)	17 (21)	16 (20)	16 (20)	12 (15)	12 (15)	10 (13)
Unable to perform normal duties					39 (49)	34 (43)	11 (14)	21 (26)

results are in table I. The χ^2 test with Yates' correction was used to evaluate the significance of differences between the two groups. The "in hospital" morbidity of those who failed to return the form was similar to that of the patients who did reply.

The most frequent symptom after operation was abdominal pain, followed by drowsiness, backache, dizziness, headache and nausea. Pain at the site of injection was significantly more common ($P<0.01$) after Althesin. There were no other significant differences in morbidity between the groups at any time ($P>0.05$).

The mean duration of surgery was 9.16 min for the Althesin group and 9.20 min for the thiopentone/halothane group, but the recovery time after Althesin was significantly shorter (Wilcoxon rank sum test, $P<0.001$) (fig. 1). Thirty-nine per cent of the Althesin group and 43% of the thiopentone/halothane group were unable to undertake their normal activities on the 1st day after operation. The corresponding figures for the 2nd day were 14% and 26%. These differences are not significantly different for both days. Nineteen patients (24%) in the Althesin group and 16 (20%) in the thiopentone/halothane group would have preferred to have been an inpatient.

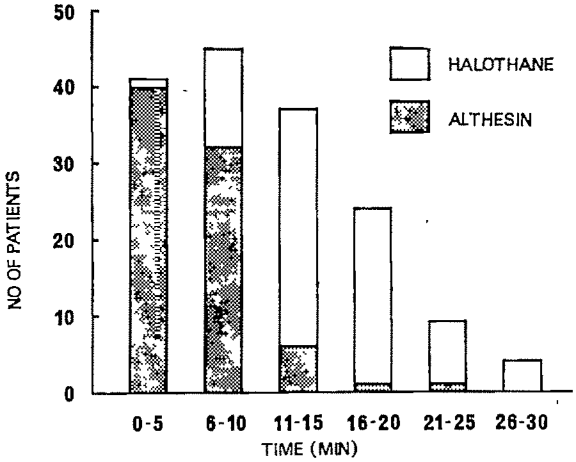

FIG. 1. The number of patients recovering during each 5-min period following the end of surgery.

DISCUSSION

The large frequency of postoperative morbidity following day-case gynaecological surgery was unexpected. We were surprised that many symptoms persisted into the 1st and 2nd days after operation and that a large number of patients were unable to carry out their normal activities at those times. Other studies (Fahy and Marshall, 1969; Ogg, 1972; Smith and Young, 1976) have reported a high frequency of morbidity, but in patients undergoing more extensive surgical procedures. To our knowledge, this is the first detailed investigation of morbidity following day-case gynaecological surgery. Although day-case surgery is an expanding and popular practice it is notable that 22% of patients would have preferred to have been an inpatient. Our Althesin technique produced a shorter recovery time than the alternative, but this does not contribute significantly to the efficient running of the outpatient theatre as all our patients remain in the recovery ward until they feel ready to walk. They remain in hospital for a minimum of 2 h after recovery. The shorter recovery time following Althesin was not reflected in any difference in the frequency of drowsiness or dizziness on leaving hospital or in the next 2 days. The shorter recovery time following Althesin must be weighed against the possibility of serious hypersensitivity reactions which occur in a small number of patients following Althesin.

The greater frequency of pain at the injection site in the group receiving Althesin may be explained by the use of an indwelling needle in the dorsum of the hand for supplementary injections (Briscoe and Taylor, 1974).

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MORBIDITE SE PRODUISANT PENDANT LE JOUR A LA SUITE D'UNE INTERVENTION CHIRURGICALE GYNECOLOGIQUE

Comparaison du thiopentone et de l'althésine

RESUME

Pour comparer deux techniques d'anesthésie, on a évalué sur 170 patientes la morbidité qui se produit pendant le jour à la suite d'une intervention chirurgicale gynécologique, à l'aide d'un questionnaire qu'on leur a fait remplir au moment oú elles quittaient l'hôpital, et qui concernait le soir de l'opération ainsi que le premier et le second joue après l'intervention chirurgicale. Quatre-vingt-quatorzu pour cent des patientes ont rempli ce questionnaire. Il y a etr une fréquence élevée de morbidité, celle-ci se prolongean jusque dans le courant de la seconde journée après l'opération. La technique d'anesthésie basée sur l'Althésine et le protoxyde d'azote dans l'oxygène n'a présenté aucun avantage par rapport à celle basée sur le thiopentone et le protoxyde d'azote dans l'oxygène et l'halothane.

MORBIDITÄT BEI FÄLLEN AMBULANTER GYNÄKOLOGISCHER CHIRURGIE

Ein Vergleich zwischen Thiopenton und Althesin

ZUSAMMENFASSUNG

Zum Vergleich von zwei Narkosemethoden wurde die Morbidität nach ambulanten gynäkologischen Eingriffen bei 170 Patienten mittels eines Fragebogens untersucht—für die Ziet des Verlassens des Krankenhauses, für den Abend der Operation und fur den 1. und 2. Tag nach der Operation. Vierundneunzig Prozent der Patienten füllten die Fragebogen aus. Es gab eine grosse Häufigkeit von Morbiditat bis in den 2. Tag nach der Operation. Eine Narkosemethode mit Althesin und Stickoxyd in Sauerstoff ergab keinen Vorteil gegenüber einer Methode mit Thiopenton und Stickoxyd in Sauerstoff und Halothan.

MORBOSIDAD DE CIRUGIA GINEACOLOGICA EN CASOS DE DIA

Una comparación entre tiopentona y Altesina

SUMARIO

A fin de comparar dos técnicas anestésicas, se evaluó la morbosidad que en casos de día siguió a la cirugía gineacológica en 170 pacientes por medio de un cuestionario completado al abandonar el hospital, en que se refería a la tarde de la operación y al primer y segundo día después de la operación. Noventa y cuatro por ciento de los pacientes entregó el cuestionario. Se produjo una elevada frecuencia de morbosidad que se extendió al segundo día después de la operación. Una técnica anestésica en que se empleó Altesina y óxido nitroso en oxígeno no presentó ventaja alguna sobre una técnica con tiopentona y óxido nitroso en oxígeno y halotano.

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HAEMOPTYSIS FOLLOWING INSERTION OF A SWAN–GANZ CATHETER

E. M. KRANTZ AND J. F. VILJOEN

SUMMARY

Haemoptysis occurred in a patient in whom a Swan–Ganz catheter was inserted for the induction of anaesthesia for hemicolectomy. It is suggested that acute pulmonary hypertension, superimposed on existing chronic pulmonary hypertension associated with mitral stenosis, was an important aetiological factor in the haemoptysis.

The introduction of the flow-directed balloon-tipped catheter by Swan and others (1970) has made possible the measurement of filling pressures in the left side of the heart. Before the introduction of the Swan–Ganz catheter, central venous pressure (c.v.p.) measurements were used to assess changes in intravascular volume and cardiac performance. However, even in the absence of cardiopulmonary disease, c.v.p. often does not correlate with pressures on the left side of the heart (Forrester et al., 1971).

Fortunately the complication rate associated with insertion of the Swan–Ganz catheter is low. However, complications do occur occasionally, with potentially fatal sequelae. Haemoptysis following insertion of a Swan–Ganz catheter is reported.

CASE REPORT

A 68-year-old white male presented with a 2-month history of dyspnoea on minimal effort, associated with progressive weakness. He was found to be in cardiac failure with an increased jugular venous pressure, hepatomegaly of 3 cm and ankle oedema. The heart rate was 110 beat min^{-1} and regular, and systemic arterial pressure was 110/80 mm Hg. Fifteen months previously he had undergone open-heart surgery comprising insertion of mitral valve (Starr–Edwards) and aortic valve (porcine) prostheses for subacute bacterial endocarditis. Subsequently, he was maintained on therapy comprising digoxin 0.125 mg daily, frusemide 80 mg daily, potassium chloride 40 mmol t.i.d., spironolactone 25 mg b.d. and warfarin 7.5 mg daily.

On this admission he was found to have a haemoglobin concentration of 6 g dl^{-1} with a haematocrit of 22% and evidence of a hypochromic and microcytic anaemia. The e.c.g. revealed an old anterior myocardial infarct and occasional unifocal ventricular premature beats. Chest x-ray showed cardiomegaly and bilateral pleural effusions. Blood-gas analysis before operation was as follows: pH 7.50 unit, $P\text{O}_2$ 9.33 kPa, $P\text{CO}_2$ 4.67 kPa.

A carcinoma of the colon was demonstrated by barium enema and the patient was submitted to hemicolectomy. Before operation one unit of packed red cells was given on alternate days and after 3 units the patient's haematocrit was 30%. Warfarin was discontinued 3 days before operation and on the day before surgery the prothrombin time and partial thromboplastin time were both normal.

It was decided to insert a Swan–Ganz catheter before the induction of anaesthesia for the following reasons: (1) the patient had unstable cardiovascular function during his previous cardiac surgery and had developed total heart block requiring temporary pacing; (2) the patient was admitted to hospital in cardiac failure; (3) fluid balance problems in the peri-operative period were anticipated in view of the nature of the proposed operation and the patient's poor cardiac reserve; (4) a central venous pressure catheter would probably not reflect accurately changes in the left side of the heart.

The right radial artery was cannulated and an initial pressure of 130/38 mm Hg recorded. The patient was placed in the Trendelenburg position and the right internal jugular vein cannulated using a 14-gauge needle and an 8 FG percutaneous catheter introducer set was inserted. A 7 FG Swan–Ganz

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catheter was advanced slowly into the right atrium. The patient was placed in a slightly head-up position. The balloon was then inflated with 1.0 ml of air and the catheter advanced further. A right ventricular pressure of 50/5 mm Hg was recorded and a pulmonary arterial pressure of 40/15 mm Hg. After the catheter had been inserted 51 cm a wedge pattern was obtained and a wedge pressure of 18 mm Hg was recorded. Following removal of the introducer, the Swan–Ganz catheter was noted to have advanced an additional 4 cm.

In addition, although the balloon was deflated, the oscilloscope tracing continued to reveal a "wedge pattern". The deflated catheter was withdrawn 1 cm at a time for a total of 5 cm, but the tracing continued to demonstrate a "wedge pattern". At this time, the patient began coughing and within 3 min coughed up bright red blood. He was immediately placed in the Trendelenburg position and the Swan–Ganz catheter removed. One hundred per cent oxygen was administered via a face mask and morphine 5 mg was administered i.v. A second peripheral i.v. cannula was inserted and 2 units of packed red cells given rapidly.

The patient coughed up a total of 250–300 ml of bright red blood over a 30-min period, but vital signs remained stable throughout and he was transferred to the intensive care unit. The patient continued to cough up small amounts of bright red blood for 7 days, but not exceeding 20 ml per day. Chest x-rays revealed a small infiltrate in the periphery of the right middle lobe.

Ten days after the initial episode the patient returned to the operating theatre. It was decided not to use a Swan–Ganz catheter, although a central venous line was placed. An uneventful hemicolectomy was performed.

DISCUSSION

Haemoptysis is an infrequent complication following the insertion of a Swan–Ganz catheter. Only five cases have been reported previously, in which haemoptysis was not attributed to pulmonary infarction (Chun and Ellestad, 1971; Lapin and Murray, 1972; German, Allyn and Bartlett, 1973; Golden et al., 1973; Page, Teres and Hartshorn, 1974).

Haemoptysis (unassociated with pulmonary infarction) has been attributed in previous cases to perforation of a pulmonary vessel. In a fatal case of haemoptysis Golden and others (1973) found at autopsy a triangular tear in the distal bifurcation of the right pulmonary artery. Following removal of the intact left lung and pulmonary artery passage of a Swan–Ganz catheter to the same position as the right pulmonary artery tear produced a similar tear on the left after inflation of the balloon.

In our patient, perforation of a pulmonary vessel could have occurred when the catheter migrated 4 cm distally, after the wedge position was attained.

Lapin and Murray (1972) believed that the presence of a gradient between mean pulmonary arterial pressure and mean capillary wedge pressure may result in movement of a catheter distally, resulting in perforation of the vessel. Our patient had a small mean pulmonary artery to wedge pressure gradient of 5 mm Hg. Both Lapin and Murray (1972) and Page, Teres and Hartshorn (1974) reported the blood in the haemoptysis to be bright red as in our patient. If the cause were perforation of a pulmonary artery, one might expect the colour to have been dark (mixed venous blood). However, it is conceivable that blood may become oxygenated in the alveoli and airways before being coughed up.

Three of the five patients reported (Lapin and Murray, 1972; Golden et al., 1973; Page, Teres and Hartshorn, 1974) had mitral stenosis. Our patient also had pulmonary hypertension, which is a well-recognized cause of haemoptysis.

We suggest, therefore, that acute pulmonary hypertension (superimposed on existing chronic pulmonary hypertension) is an important aetiological factor in haemoptysis following insertion of a Swan–Ganz catheter.

The management of severe haemoptysis poses several problems including the control of bleeding, the maintenance of ventilation and maintenance of an adequate circulation. Fortunately, in our patient these problems were not severe. In the severe case the use of a double-lumen tube may be life-saving by permitting adequate ventilation of one lung.

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HEMOPTYSIE APRES INSERTION D'UN CATHETER DE SWAN–GANZ

RESUME

Il s'est produit une hémoptysie chez un patient auquel on avait introduit un cathéter de Swan–Ganz pour induction de l'anesthésie, avant de procéder à une hemicolectomie. On pense qu'une tension pulmonaire aigüe ajoutée à l'hypertension pulmonaire chronique existante associée à une sténose mitrale, ont été un important facteur étiologique de cette hémoptysie.

HÄMOPTYSIS NACH EINFÜHRUNG EINES SWAN–GANZ-KATHETERS

ZUSAMMENFASSUNG

Hàmoptysis trat bei einem Patienten auf, dem zur Einleitung von Narkose für eine Hemikolektomie ein Swan–Ganz-Katheter eingeführt wurde. Es wird behauptet, dass eine akute pulmonare Hypertension, zusätzlich zu einer vorhandenen chronischen pulmonaren Hypertension im Zusammenhang mit Mitralstensoe, ein wichtiger ätiologischer Faktor in der Hamoptisis ist.

HEMOPTISIS SIGUIENDO LA INSERCION DE UNA SONDA SWAN–GANZ

SUMARIO

Se produjo hemoptisis en un paciente a quien se le introdujo una sonda Swan–Ganz con el fin de inducir anestesia para hemicolectomía. Se sugiere que la hipertensión pulmonar aguda, superpuesta a la hipertensión pulmonar crónica existente en associación con estenosis mitral, fue un importante factor etiológico en la hemoptisis.

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SYSTEMIC AIR EMBOLISM FOLLOWING INDUCTION OF ARTIFICIAL PNEUMOTHORAX UNDER ANAESTHESIA, WITH SUCCESSFUL MANAGEMENT

S. N. KHALIL, V. MADAN, B. M. RIGOR, W. S. FIELDS AND K. M. UNGER

SUMMARY

Systemic air embolism occurred in a patient during general anaesthesia, with positive pressure ventilation, following induction of artificial pneumothorax to assist in the diagnosis of a mediastinal mass. A sudden change in vital signs together with neurological abnormalities suggested involvement of both coronary and cerebral arteries. A trace of blood was noticed in the syringe which the surgeon had used to create the artificial pneumothorax. The patient was treated with hyperbaric oxygen and recovered satisfactorily, despite a 10-h interval between the air embolus and the institution of definitive therapy.

Air embolism may occur in the pulmonary or systemic circulations. Systemic air embolism can occur as a complication of cardiopulmonary bypass, therapeutic pneumothorax, haemodialysis and paradoxical air embolism through a patent foramen ovale. Thomas and colleagues (Thomas and Roe, 1973; Thomas and Stephen, 1974) demonstrated both experimentally and clinically that a penetrating injury to the lung may produce an acute broncho–venous fistula resulting in arterial air embolism, particularly when positive pressure ventilation is being used. Arterial air embolism from broncho–venous fistulae has also been reported from lung penetration during thoracocentesis (Van Bahr, 1944) and lung biopsy (Youmans et al., 1970).

The authors encountered a similar situation in a patient who was undergoing induction of artificial pneumothorax for diagnostic purposes under general anaesthesia with positive pressure ventilation.

CASE REPORT

A 23-year-old healthy white male was admitted to hospital with a middle mediastinal mass projecting into the left lung field, detected on a routine chest x-ray. The patient was to undergo bronchoscopy oesophagoscopy and possible left thoracotomy.

Premedication consisted of pethidine 75 mg, hydroxyzine pamoate 50 mg, and atropine 0.5 mg, all administered i.m. 1 h before operation. Anaesthesia was induced with thiopentone 300 mg i.v. and maintained with halothane 1–2%, and nitrous oxide in 50% oxygen. Suxamethonium 100 mg was given to facilitate endotracheal intubation, using a cuffed Portex orotracheal tube (8.5 mm) and neuromuscular blockade was maintained with an i.v. infusion of suxamethonium. Ventilation was controlled manually.

Both fibreoptic bronchoscopy and oesophagoscopy were uneventful and uninformative.

To assess the relationship of the mediastinal mass to the surrounding structures, the surgeon induced a left artificial pneumothorax, before which nitrous oxide was discontinued. The surgeon used an 18-gauge spinal needle, a 60-ml syringe and a three-way stopcock. A trace of blood was noticed in the syringe following aspiration. After repositioning the needle, 150 ml of air was injected over 1 min into the left side of the chest in the anterior axillary line, just below the nipple.

Suddenly, the pattern of the e.c.g. changed from sinus rhythm to severe bradycardia, with intraventricular conduction defect and idioventricular rhythm. This was accompanied by a transient decrease in arterial pressure from 130/90 mm Hg to 90/50 mm Hg. Heart sounds became muffled. Patchy areas of cyanosis developed over the neck and the upper chest. Halothane and suxamethonium infusion were discontinued, but the patient developed generalized rigidity,

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decerebrate posturing, extreme restlessness and tachypnoea; the endotracheal tube started to leak and became displaced, necessitating removal of the tube and administration of oxygen by mask.

The e.c.g., arterial pressure and skin colour returned to normal within 3–5 min but the patient failed to regain consciousness. The pupils were constricted, equal and reactive. Diazepam 5 mg was given for sedation, but did not have a demonstrable effect.

Arterial blood-gas analysis revealed pH 7.3 unit, $P\text{CO}_2$ 5.9 kPa, $P\text{O}_2$ 17.7 kPa, standard bicarbonate 21 mmol litre^{-1} and base excess −5 mmol litre^{-1}. Serum calcium was 6.7 mg dl^{-1}. Sodium bicarbonate 44.6 mmol and calcium chloride 1.0 g were given i.v. An erect chest x-ray showed minimal air in the left apical pleural space.

The patient was moved to the recovery room in a head-down position; after repeated blood-gas studies, it was possible to reduce $F\text{I}_{\text{O}_2}$ to 50%, administered from a venturi mask.

The patient remained comatose and decerebrate, with tachypnoea. On retinoscopy, the fundi were pale, but there was no air in the vessels. The e.e.g. showed dominant activity slower than normal throughout, but there was marked asymmetry with slower frequencies over the left hemisphere compared with the right, suggesting major left hemisphere dysfunction. A neurologist made a diagnosis of brain stem ischaemia secondary to cerebral air embolism.

There was a clicking sound at the left sternal border with respiration, probably resulting from pneumomediastinum or pneumothorax. The patient continued to have intermittent bradycardia and brief periods of apnoea. He remained unconscious, extremely restless, trachypnoeic and quadriplegic and was apparently deteriorating.

The patient was transported to a nearby hyperbaric unit by the hospital helicopter which flew at an altitude of less than 305 m. He was initially treated according to a modification of the U.S. Navy Table 6A, with initial compression to 61 m (7 atm abs.). The patient was more responsive within 20 min of compression. The U.S. Table 6A recommends rapid compression (in less than 2 min) to 50 m (6 atm abs.), then, after 30 min, ascent to 18.3 m (2.8 atm abs.) for 90 min of intermittent hyperbaric oxygen breathing, followed by ascent to 9 m (1.9 atm abs.) for 195 min of further intermittent oxygen.

Hyperbaric oxygenation treatment was continued during the next week with an excellent neurological recovery. The patient regained consciousness on the 6th day. After 1 week, dysphasia and right hemiparesis were still present. The speech defect diminished to the point at which difficulty with finding words was apparent only when the patient was fatigued or under stress. The hemiparesis persisted for approximately 2.5 months. An intention tremor of both hands, more marked in the right, persisted for 11 months after the incident.

DISCUSSION

Systemic embolism following penetrating lung trauma has been appreciated only recently. Forlanini first advocated artificial pneumothorax for therapy of pulmonary tuberculosis (Schlaepfer, 1922). After this procedure became popular, numerous cases of "pleural shock" were reported (Van Allen, Hrdina and Clark, 1929). Some deaths occurred after the introduction of a needle into the thoracic cavity before any air was injected (Reger and Kohl, 1926), presumably because the needle had injured the lung parenchyma. In 1899 Murphy suggested that air embolism might be the cause of pleural shock (Schlaepfer, 1922). Brauder reported a case in which the pulmonary veins were shown to be the portal of entry for air embolism (Schlaepfer, 1922).

The importance of air embolism following penetrating lung trauma was not fully recognized until Thomas and others (Thomas and Roe, 1973; Thomas and Stephen, 1974), in both clinical and experimental studies, demonstrated that air could pass from the pulmonary to the systemic circulation. It is well known that the entrance of air into the pulmonary veins can be fatal by producing systemic embolism of cerebral and coronary vessels (Geoghegan and Lam, 1953).

Experimentally, cerebral air embolism is fatal when 0.5–1.5 ml kg^{-1} of air is injected into the cerebral circulation (Fries et al., 1957). Similar experiments with coronary air embolism have shown that 0.05 ml of air injected into the left anterior descending artery or 1.5 ml into the left ventricle is fatal (Rukstinat, 1931). Relatively large amounts of air (5–8 ml kg^{-1}) may be tolerated in the venous circulation (Durant et al., 1949).

It has been falsely assumed that venous embolism is relatively harmless because the pulmonary capillaries are efficient air filters (Durant et al., 1949). However, Spencer and Oyama (1971) showed that air can cross the pulmonary capillaries when the pulmonary artery pressure exceeds 29 mm Hg. Air in the venous side can also pass to the arterial side through a patent foramen ovale. The frequency of patent foramen ovale is found to be as high as 25% in some autopsy series (Van Allen, Hrdina and Clark, 1929).

The principal symptoms of arterial air embolism are those resulting from involvement of the coronary, cerebral and renal arteries. The position of the patient at the time of embolization affects the distribution of emboli. Air embolism is associated with sudden changes in vital signs and usually presents with widespread clinical manifestations.

In the case reported here, the sudden changes in vital signs and failure to regain consciousness, together with the appearance of a trace of blood in the syringe on aspiration, led us to the diagnosis of air embolism. The patient showed evidence of coronary emboli, manifested by a sudden decrease in arterial pressure, muffled heart sounds and appearance of slow wide QRS complexes on the e.c.g.

Frank convulsions were not noted because the patient was paralysed, but as soon as the suxamethonium infusion was discontinued, it was extremely difficult to ventilate the lungs. The patient then started to assume a decerebrate posture with opisthotonus. The marked tachypnoea was thought to be a reflection of cerebral involvement. Failure to regain consciousness after operation was further evidence of cerebral involvement, but the fact that he improved within 20 min of initial compression treatment was diagnostic of cerebral embolism.

Artificial pneumothorax should not be created under anaesthesia, particularly with positive pressure ventilation. Embolism should be suspected if the patient shows sudden changes in vital signs. If nitrous oxide is used, it should be discontinued immediately as it can lead to an increase in the size of the air bubbles.

If air embolism occurs, the patient should be turned on to his left side in a head-down position in order to keep the bubbles of air away from the pulmonary outflow tract. An attempt should be made to aspirate the air when possible. If there is evidence of penetrating lung trauma, it is wise to avoid positive pressure ventilation whenever possible. If all these measures fail, then treatment with compression to 6–7 atm abs. in a hyperbaric chamber, followed by hyperbaric oxygen therapy, is indicated (Kinwall, 1973; Thiede and Manley, 1976). This case report confirms the fact that hyperbaric therapy may still be of use even after several hours have elapsed since the onset of symptoms.

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EMBOLIE GAZEUSE SYSTEMIQUE APRES INDUCTION D'UN PNEUMOTHORAX ARTIFICIEL SOUS ANESTHESIE ET CONDUITE SATISFAISANTE DU TRAITEMENT

RESUME

Une embolie gazeuse systémique s'est produite sur un malade au cours d'une anesthésie générale, avec ventilation sous pression positive, après l'induction d'un pneumothorax artificiel devant aider au diagnostic d'une masse médiastinale. Un changement soudain dans les signes vitaux, ainsi que des anomalies neurologiques ont laissé penser à une lésion des artères coronaire et cérébrale. On a remarqué une trace de sang dans la seringue que le chirurgien avait utilisée pour créer le pneumothorax artificiel. Le malade a été soigné par oxygénothérapie hyperbare et a récupéré d'une manière satisfaisante en dépit d'un intervalle de 10 h entre l'embolie gazeuse et la mise en place d'une thérapie définitive.

SYSTEMISCHE LUFTEMBOLIE NACH INDUKTION VON KÜNSTLICHEM PNEUMOTHORAX UNTER NARKOSE, MIT ERFOLGREICHER BEHANDLUNG

ZUSAMMENFASSUNG

Bei einem Patienten trat während der Vollnarkose eine systemische Luftembolie ein, bei positiver Druckventilation, nach Induktion eines künstlichen Pneumothorax zur Unterstützung bei der Diagnose einer Masse im Mittelfell. Eine plötzliche Veränderung in den Lebenszeichen, im Zusammenhang mit neurologischen Anomalien, liess auf die Beteiligung sowohl der Herzkranzarterien als auch der Gehirnarterien schliessen. In der vom Chirurgen zur Induktion des künstlichen Pneumothorax benutzten Spritze wurde eine Blutspur festgestellt. Der Patient wurde mit Sauerstoff unter Überdruck behandelt und erholte sich trotz einer 10-stündigen Zwischenzeit zwischen der Luftembolie und Einleitung einer definitiven Therapie zufriedenstellend.

EMBOLIA SISTEMICA DE AIRE TRAS LA INDUCCION DE NEUMOTORAX ARTIFICIAL BAJO ANESTESIA, TRATADA CON EXITO

SUMARIO

Se produjo una embolia sistémica de aire en un paciente durante anestesia general, con ventilación de presión positiva, tras la inducción de neumotórax artificial para asistir en el diagnóstico de una masa mediastinal. Un cambio repentino en los signos vitales, junctamente con anormalidades neurológicas, sugirió la participación de las arterias tanto coronaria como cerebral. Se notó una traza de sangre en la jeringa que el cirujano utilizó para crear el neumotórax artificial. El paciente fue tratado con oxígeno hiperbárico y se recuperó satisfactoriamente, a pesar de un intervalo de 10 h entre la embolia de aire y el comienzo de una terapia definitiva.

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CONGENITAL FIBRO–OSSEOUS DYSPLASIA OF JAWS ("HIPPOPOTAMUS FACE")

An anaesthetic problem

J. P. KUNDU AND A. K. PAN

SUMMARY

Two brothers with "hippopotamus face" deformities presented for corrective surgery under general anaesthesia. In the first patient, blind nasal intubation was successful. In the second patient, tracheotomy was avoided by the use of an intubating bronchoscope.

An extremely rare variety of jaw tumour affecting a father and his two sons was reported by Chatterji and Mazumdar in 1967. The tumour takes the form of lobulated masses arising from the alveolar margins of the upper and lower jaws, and causes a hippopotamus-like deformity. The histological appearance is that of fibro–osseous dysplasia from extensive proliferation of the mucoperiosteum and underlying connective tissue of the jaws. This is not a neoplasm but a developmental error.

The patient described by Chatterji and Mazumdar underwent a four-stage corrective procedure under general anaesthesia preceded by tracheotomy in 1959, since when he has shown no signs of recurrence.

His two sons both developed similar progressive deformities and presented for corrective surgery in April 1978, aged 15 and 12 yr (fig. 1). Apart from their facial abnormalities, both boys were fit and well.

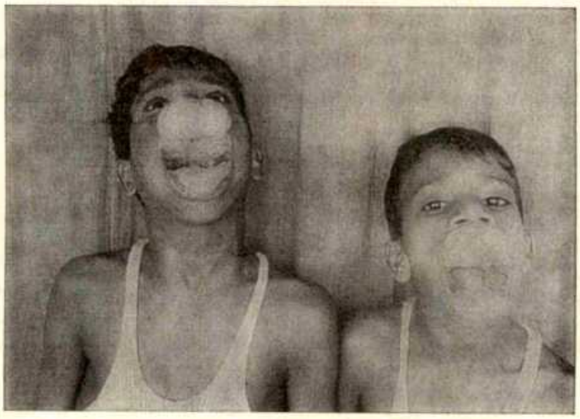

FIG. 1. The two brothers before operation.

CASE REPORTS

Case no. 1. The older brother

Both upper and lower jaws protruded well beyond the lips, which were stretched around the masses (fig. 2). The surfaces of the masses were rough and lobulated and the inner aspect like a gutter along the edge of which the teeth were buried. The masses opened like the beak of a bird and the tongue could not reach the tip of the jaw. The nostrils were reduced to mere slits. For the previous 3 months he had been unable to breathe through his nose, and although he could eat solids he had to tilt his head back to drink. Indirect laryngoscopy showed that the position and shape of the epiglottis and laryngeal inlet were normal,

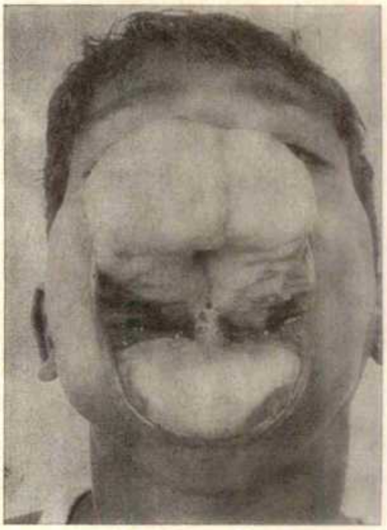

FIG. 2. The older brother (case 1) showing inside of the mouth.

J. P. KUNDU, F.F.A.R.C.S., F.F.A.R.C.S.I.; A. K. PAN, M.B., B.S.; Department of Anaesthesiology, N.R.S., Medical College, Calcutta, India.

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but direct laryngoscopy could not be achieved with the large Macintosh blade.

A good fit could be obtained with a size 4 anaesthetic face mask and breathing could be assisted easily.

Anaesthetic techniques. Before performing a preliminary elective tracheotomy, it was decided to attempt tracheal intubation either blindly or by direct laryngoscopy. Premedication was with diazepam 15 mg i.m. 30 min before induction of anaesthesia. After an i.v. infusion had been set up, atropine 0.65 mg was administered i.v. and anaesthesia was induced with nitrous oxide, oxygen and halothane. A 5.5-mm streamlined cuffed nasal endotracheal tube was passed blindly without difficulty. Gallamine 3.5 mg kg^{-1} was administered, and ventilation was controlled. Anaesthesia was maintained with nitrous oxide and oxygen alone.

At the end of the procedure residual paralysis was antagonized with atropine and neostigmine, and when the patient was fully awake the tracheal tube was removed after pharyngeal and endotracheal aspiration.

Surgery involved chiselling of the tumour back to the alveolar margins and extraction of the teeth, and resulted in considerable blood loss. The operation was performed in four stages at 2- or 3-weekly intervals and on each occasion blind nasotracheal intubation was performed without difficulty. Blood loss was replaced by transfusion.

Case no. 2. The younger brother

This boy's clinical features were very similar to those of his brother, except that the masses were not so large and there was no nasal obstruction (fig. 3). He could eat solids, but could take liquids only with a spoon. Again, direct laryngoscopy was impossible, but a size 4 mask fitted well over the face. Surgery was planned in four stages and it was decided to try to avoid tracheotomy. Premedication and induction were the same as in the first case, but attempted blind nasal intubation was unsuccessful. The operation was postponed until the next day. On this occasion, when anaesthesia had been induced and the jaw was relaxed, a child's intubating bronchoscope over which a 5.5-mm cuffed endotracheal tube had been threaded was introduced into the mouth and passed through the larynx to the trachea. The bronchoscope was withdrawn and anaesthesia proceeded as in case 1.

This procedure was followed for the next two stages (fig. 4), but at the fourth stage intubation could be performed under direct vision.

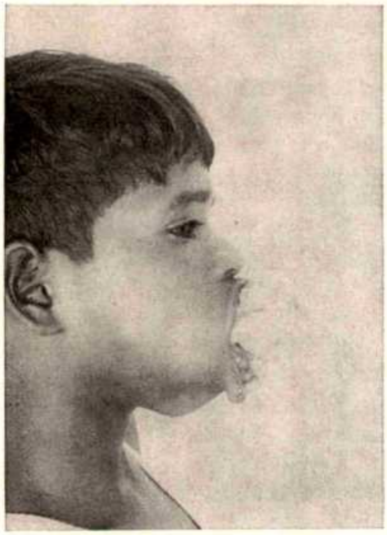

FIG. 3. The younger brother (case 2), lateral view.

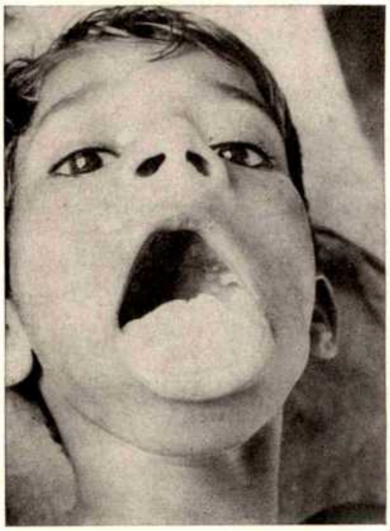

FIG. 4. The younger brother after the second stage of operation.

DISCUSSION

Fibro–osseous dysplasia of the jaw is a very rare variety of congenital deformity. We have experience of three cases, but the children of these patients may present for similar surgery. Preliminary tracheotomy is a safe approach, and we may have exposed our patients to unnecessary risk. In the first case we were fortunate to succeed with blind nasal intubation. The use of the intubating bronchoscope is not new, but we did not consider it until the failure of blind nasal intubation in the second case. We would like to point out that this neglected technique, apart from its usual role in the placement of an endobronchial tube, may often succeed in a difficult situation such as this when conventional methods have failed and costly instruments like fibreoptic endoscopes are not available.

ACKNOWLEDGEMENTS

We should like to thank the Superintendent, N.R.S., Medical College Hospitals, for permission to use hospital records; Professor S. K. Chatterji for permission to report on patients under his care; and Drs A. K. Nandy, S. Das and D. Basak and the Operating Theatre Sisters for extending their help and co-operation in preparing this case report. Dr Oliver Bastard helped with the writing of the manuscript.

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DYSPLASIE FIBRO-OSSEUSE CONGENITALE DES MACHOIRES "GUEULE DE LOUP"

Problème d'anesthésie

RESUME

Deux frères ayant des difformités du type "gueule de loup" se sont présentés pour chirurgie esthétique sous anesthésie générale. Sur le premier patient, l'intubation nasale à l'insu a été couronnée de succès. Dans le second cas, on n'a pu éviter la trachéotomie qu'en utilisant un bronchoscope de tubage.

ANGEBORENE OSTEOFIBRÖSE DYSPLASIE DES KIEFERS ("NILPFERDGESICHT")

Ein narkose-problem

ZUSAMMENFASSUNG

Zwei Brüder mit "Nilpferdgesicht"-Deformierungen wurden korrigierenden chirurgischen Eingriffen unter allgemeiner Narkose unterzogen. Beim ersten Patienten war eine blinde Nasal-Intubation erfolgreich. Beim zweiten Patienten wurde Tracheotomie durch Verwendung eines eingeführten Bronchoskops vermieden.

DISPLASIA FIBRO-OSEA CONGENITA EN LAS QUIJADAS ("CARA DE HIPOPOTAMO")

Un problema anéstesico

SUMARIO

Dos hermanos con deformidades de "cara de hipopótamo" se presentaron para cirugía correctiva bajo anestesia general. En el primer paciente se realizó con éxito una intubación nasal ciega. En el segundo paciente, se evitó la necesidad de traqueotomía mediante el empleo de un broncoscopio de intubación.

Br. J. Anaesth. (1979), **51**, 469

CORRESPONDENCE

ADVERSE REACTIONS TO I.V. AGENTS

Sir,—We have previously invited all anaesthetists who see an anaphylactoid type of adverse response in a patient following administration of an i.v. hypnotic to contact us and to take blood samples following a simple protocol (Watkins, Thornton and Clarke, 1976). The response to date (almost 100 cases) has been very good and we express again our appreciation to those anaesthetists who have made the effort to forward the necessary samples.

The clinical features of the adverse (anaphylactoid) response, which may include cutaneous (urticaria and flushing), pulmonary (bronchospasm) and cardiovascular (hypotension) manifestations are predominantly a result of the release of histamine and are not diagnostic of an anaphylactic (Type I, IgE-mediated) reaction. We are now aware of several mechanisms by which this may occur *in vivo* without involving IgE antibodies. Indeed, relatively few adverse reactions to any i.v. compound involve antibodies in a classical manner and we therefore view the claims made for skin-testing with a great deal of scepticism, since they must of necessity pre-judge the mechanism of the reaction. Although imperfect, examination of changes in plasma factors such as complement, the immunoglobulins in general, and IgE specifically, does not pre-judge the mechanism of the reaction.

As a result of these investigations we are now reaching an understanding of the various mechanisms of the anaphylactoid response and, perhaps more important, of the factors predisposing to such response (Watkins, 1979).

Not all reactions involve the induction agent itself. Anaphylactoid reactions may be induced by the neuromuscular blocking drugs or the premedication or even synergistic combinations of these. We have recently encountered a case, reported to the Committee on Safety in Medicines as a possible response to Althesin, which involved a plasma expander, Haemaccel, which is not mentioned in the adverse response report. Anaphylactoid reactions to plasma substitutes probably occur even more frequently than those to i.v. induction agents. Their clinical manifestations resemble those associated with the i.v. induction agents although urticaria and gastrointestinal disturbances appear more frequently.

We extend an invitation to all anaesthetists who see an anaphylactoid response in a patient following administration of *any* i.v. agent (hypnotic, muscle relaxant or plasma substitute) to take blood samples, as closely as possible following the protocol described below and to contact:

Dr J. Watkins, Protein Reference Unit,
Department of Immunology,
Hallamshire Hospital Medical School,
Sheffield S10 2RX.

Venous blood (5 ml) should be collected into an EDTA tube as soon as possible after the reaction begins. Heparinized tubes are a less satisfactory substitute but can be used in an emergency: the chemical EDTA effectively stabilizes plasma complement proteins. In view of the deterioration of complement components in blood samples it is recommended that the plasma is separated and stored at −20 to −25 °C until ready for despatch. Further 5-ml samples of EDTA blood should be taken at 3, 6 and 24 h after the reaction and another 5 ml taken, if possible, 3 days after the event. The last sample provides a convenient baseline for the patient. It would also help the investigation if further samples of blood (in EDTA tubes) are taken within 10 min of reaction, and again at 20 min, 1 h and 24 h after the reaction, and sent to the local Haematology laboratory for both white cell (total and differential) and platelet counts and for haemoglobin measurements. These simple haematological procedures will often provide useful information regarding the mechanism of the adverse response when less sensitive protein assay methods are equivocal (Watkins, Ward and Appleyard, 1977).

Full records of the incident, including batch numbers of all agents administered, should be kept and details of the previous administration of these substances and relevant history, such as allergies, should be noted.

The first series of samples (taken over 24 h) should be despatched as a single batch as soon as possible by first class mail to Dr Watkins. Packing the samples in "dry ice" is not necessary. Receipt of the blood samples will be acknowledged and results of the blood assays will be communicated as soon as they are available.

J. WATKINS
J. A. THORNTON
Sheffield
R. S. J. CLARKE
Belfast

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SURVIVAL FOLLOWING 1000 MG OF AMETHOCAINE

Sir,—A male (aged 63 yr) in good general condition was undergoing bronchoscopy under topical anaesthesia for suspected carcinoma of the bronchus. Premedication comprised pethidine 50 mg and atropine 0.5 mg administered i.m. 30 min before the procedure. The surgeon applied 20 ml of amethocaine 5% to the patient's mouth, pharynx and larynx within a 3-min period. Immediately after the insertion of the rigid bronchoscope, the patient became unconscious and developed convulsions. The anaesthetic team was summoned and the patient's trachea was intubated and the lungs ventilated with 100% oxygen. Diazepam 10 mg, mephentermine 15 mg and hydrocortisone 1.5 g were given i.v. and in 1.5 min the convulsions stopped, but 3 min later they recommenced. A second dose of diazepam 10 mg decreased the frequency and intensity of convulsions but they did not cease.

Following the administration of thiopentone 100 mg, the convulsions stopped completely and permanently. Five hours later, the patient was awake and he exhibited no neurological sequelae.

Following this episode, the surgeons have been persuaded to use amethocaine only in concentrations of 0.5 or 1.0%.

N. G. Balamoutsos
F. Alevizou-Christophoridou
Thessaloniki, Greece

EVALUATION OF ETOMIDATE

Sir,—In their paper entitled "Evaluation of three preparations of Etomidate" (Zacharias et al., 1978), the authors report a high frequency of pain on injection (30% in 145 patients).

These findings are at variance with our studies of Etomidate in 300 unpremedicated patients in outpatient anaesthesia (Hendry, Miller and Lees, 1977; Lees and Hendry, 1977; Miller, Hendry and Lees, 1978). Initially we encountered a frequency of pain on injection of 27%, but this was reduced significantly, to 14%, by increasing the rate of injection from 30 s to 15 s. Pain on injection was reduced further to 4% when the solvent was changed from saline to polyethylene glycol and the improvement was maintained in our third study, a double-blind trial comparing Etomidate in propylene glycol with methohexitone, pain on injection with methohexitone being 6%.

While we awaited either visual or auditory response from the patients before recording pain on injection, Zacharias and colleagues questioned their patients routinely as to the frequency of pain on injection. It seems unlikely that this difference in method would account for the discrepancies.

The authors also stated that an excitatory effect occurred in 70–95% of patients. This compares with our ranges of 10–22% and 0–4% in the two studies.

We believe it is important to resolve these points. In our opinion Etomidate has proved to be a most useful induction agent and may have a significant part to play in the development of total i.v. anaesthesia. At the recent 5th European Congress of Anaesthesiology, two separate references (Drs Popescu and Hermans, and Dr Van Dijk) were made regarding the value of Etomidate in these circumstances.

J. G. B. Hendry
N. W. Lees
B. M. Miller
Glasgow

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Sir,—We are grateful to Dr Hendry and his colleagues for reminding us of his findings which, inadvertently, we had omitted to discuss in our paper. There appears to be little difference of opinion over the frequency of pain on injection with the aqueous formulations and this is 30–50% in most studies (Lees and Hendry, 1977; Schuermans et al., 1978; Zacharias et al., 1978). There are fewer reports of pain with the preparation of Etomidate in propylene glycol, and here we do differ from Hendry, Miller and Lees (1977) in finding a pain frequency of 25–35%. The small frequency in the latter study may have been partly a result of failure to question the patient about pain.

The difference in frequency of excitatory effects between the findings of Dr Hendry and his colleagues and our own is more striking. One can only say that many investigators using Etomidate without premedication, halothane or i.v. supplementation with fentanyl have found a frequency of excitatory effects of about 50% or more (Holdcroft et al., 1976; Van de Walle et al., 1976; Schuermans et al., 1978). We affirm that for us there is an unacceptable frequency of excitatory effects (involuntary muscle movements or myoclonus) in the absence of opiate premedication or previous administration of fentanyl.

M. Zacharias
R. S. J. Clarke
J. W. Dundee
Belfast

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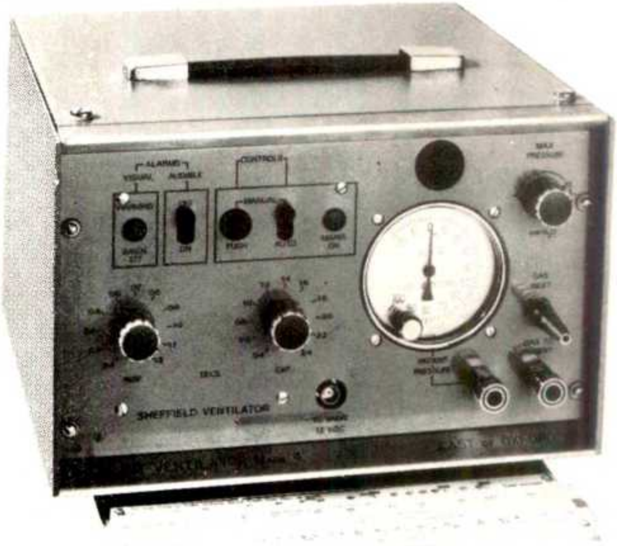

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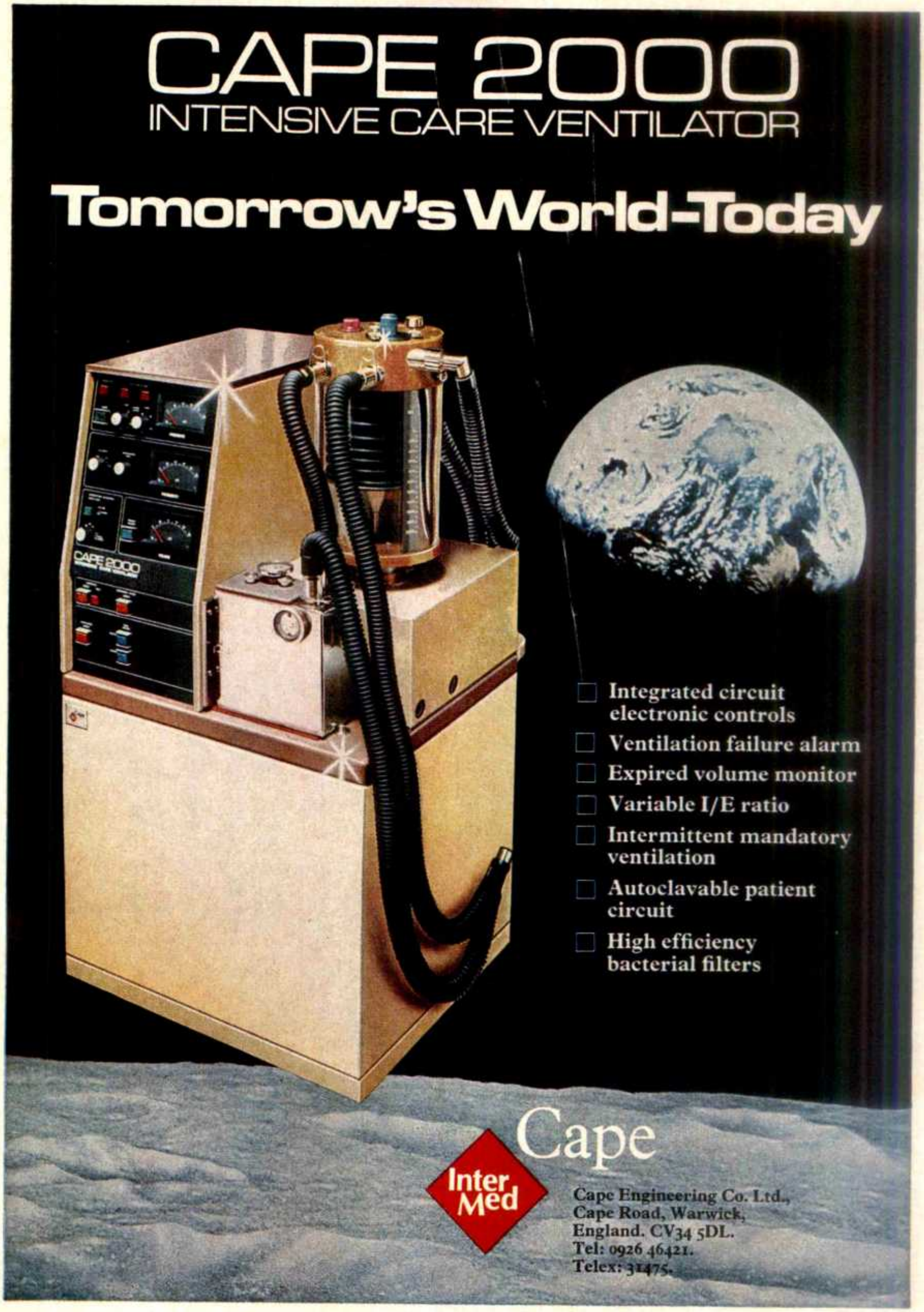

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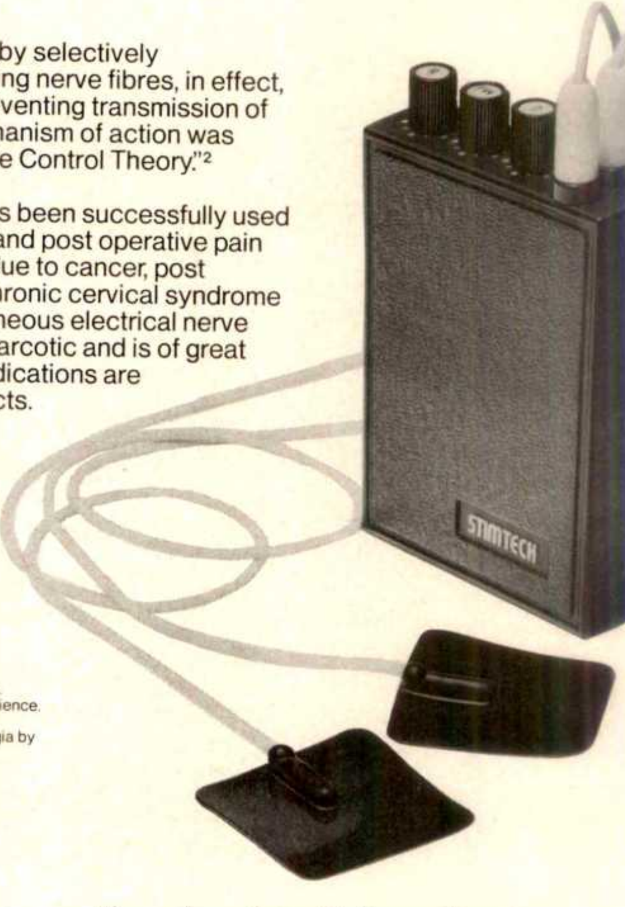

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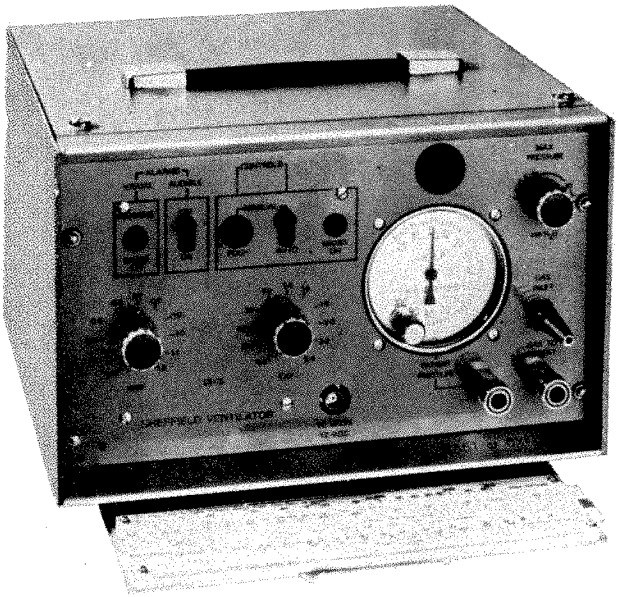

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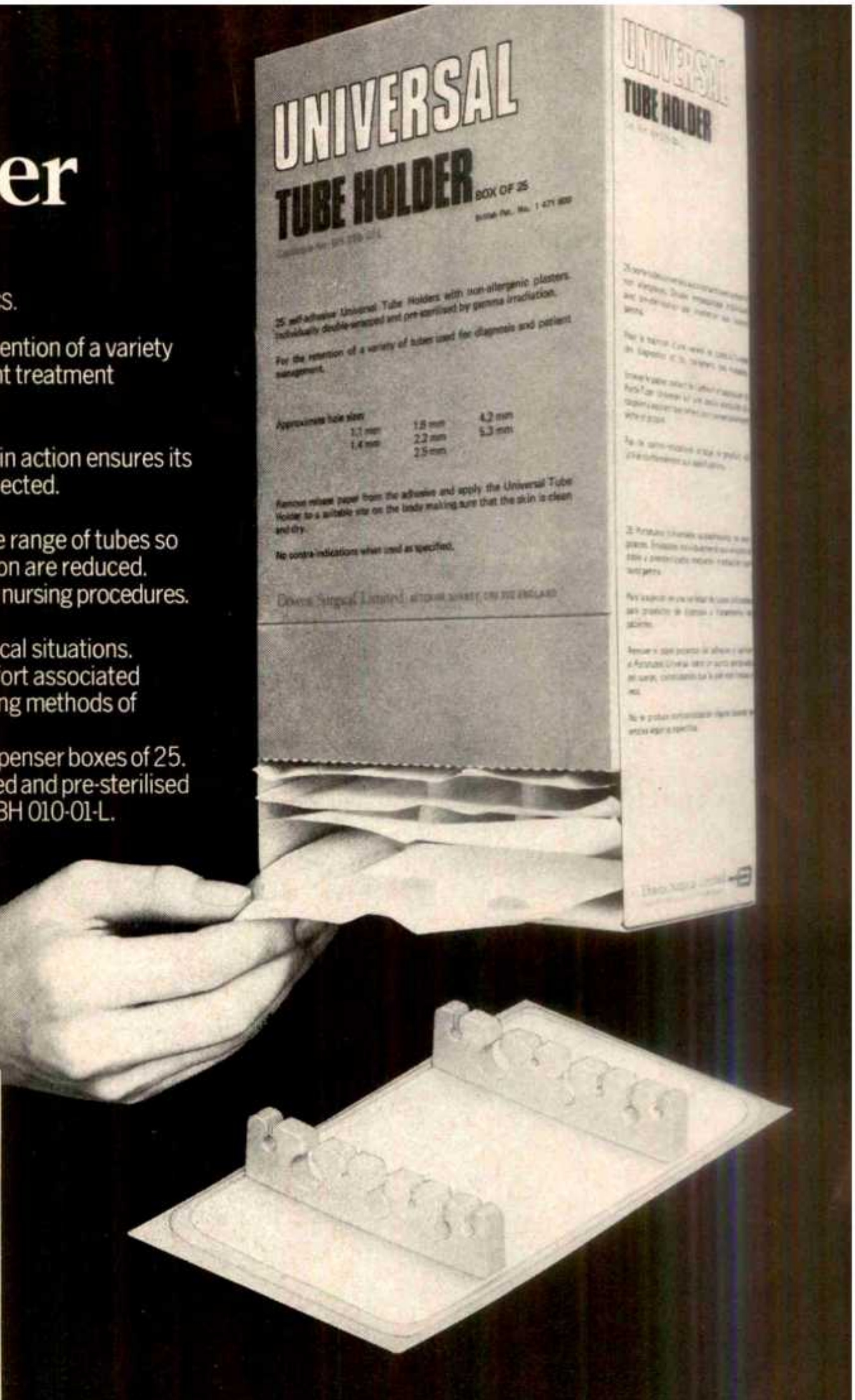

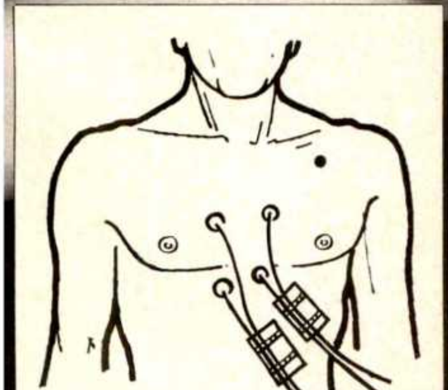

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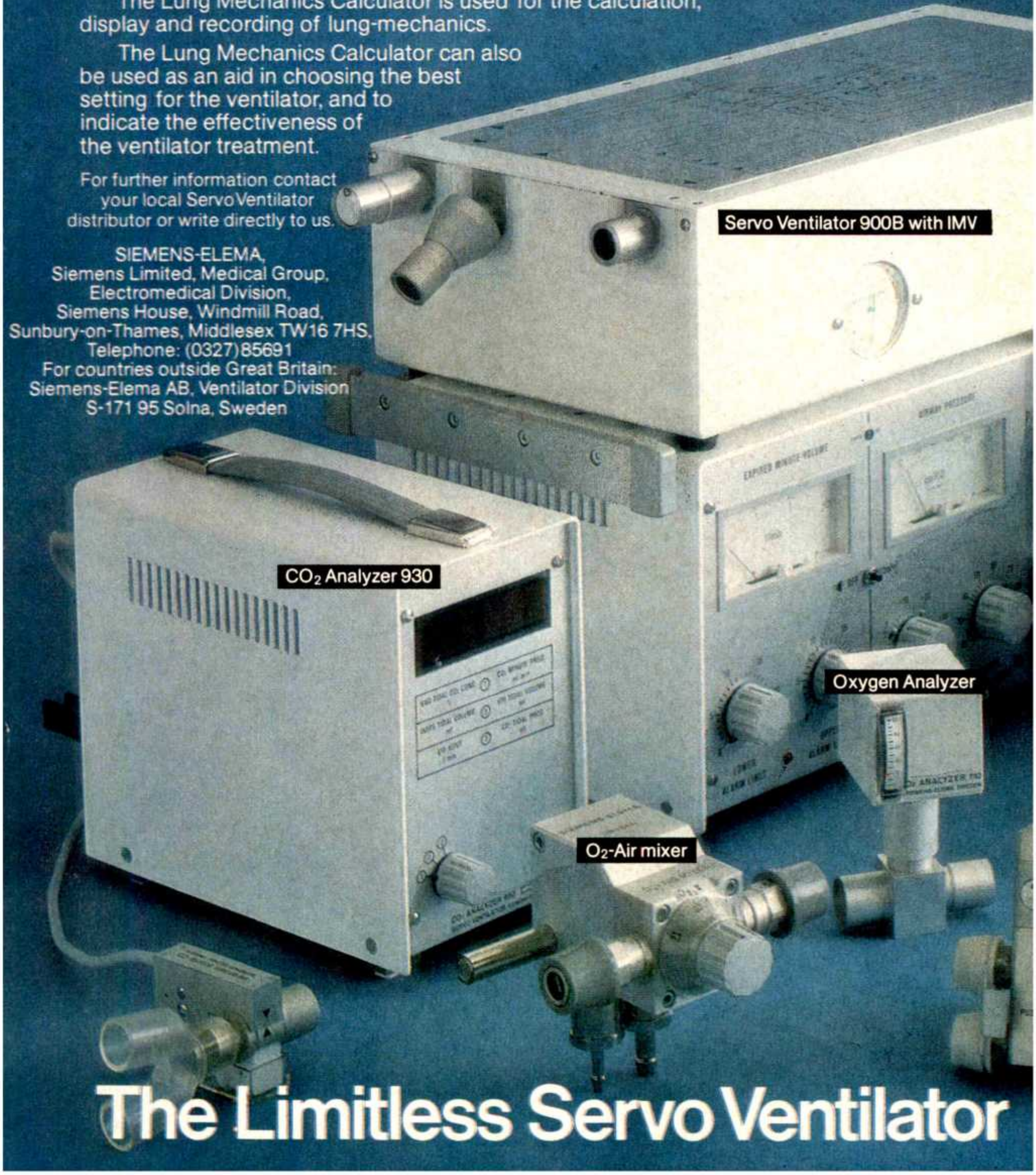

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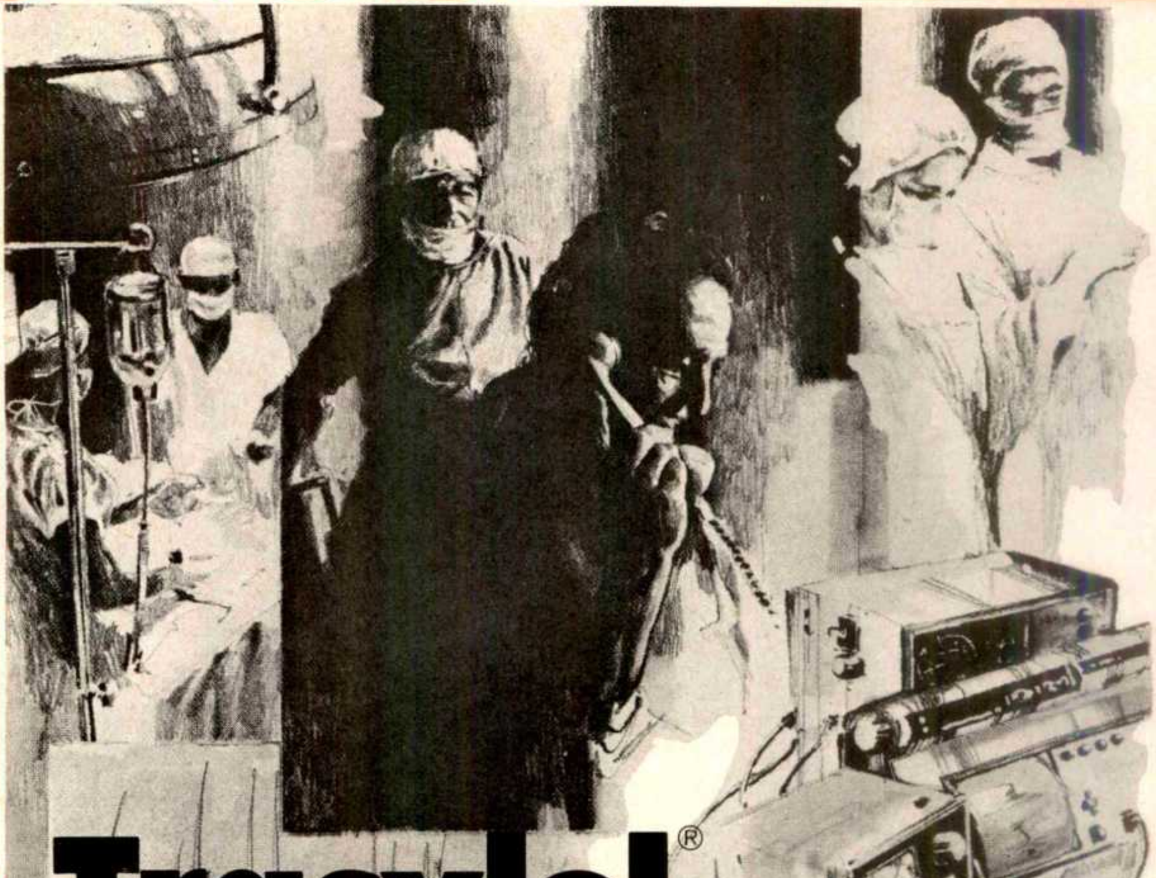

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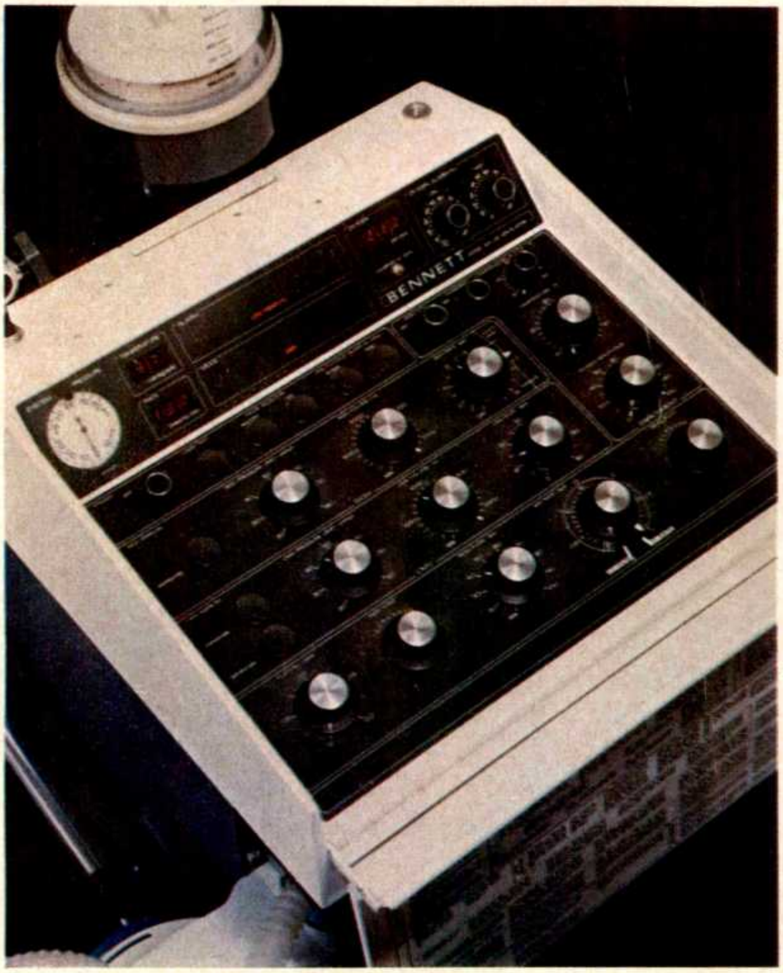

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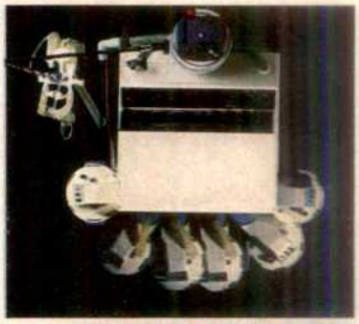

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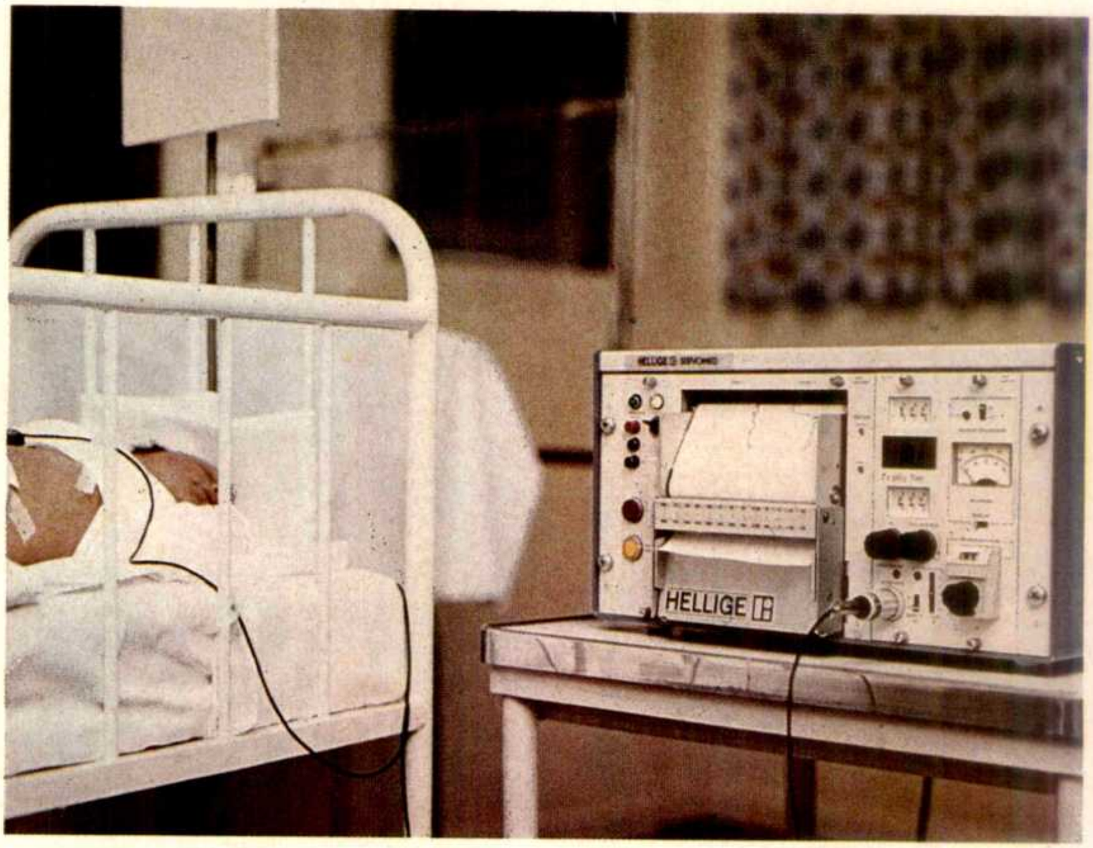

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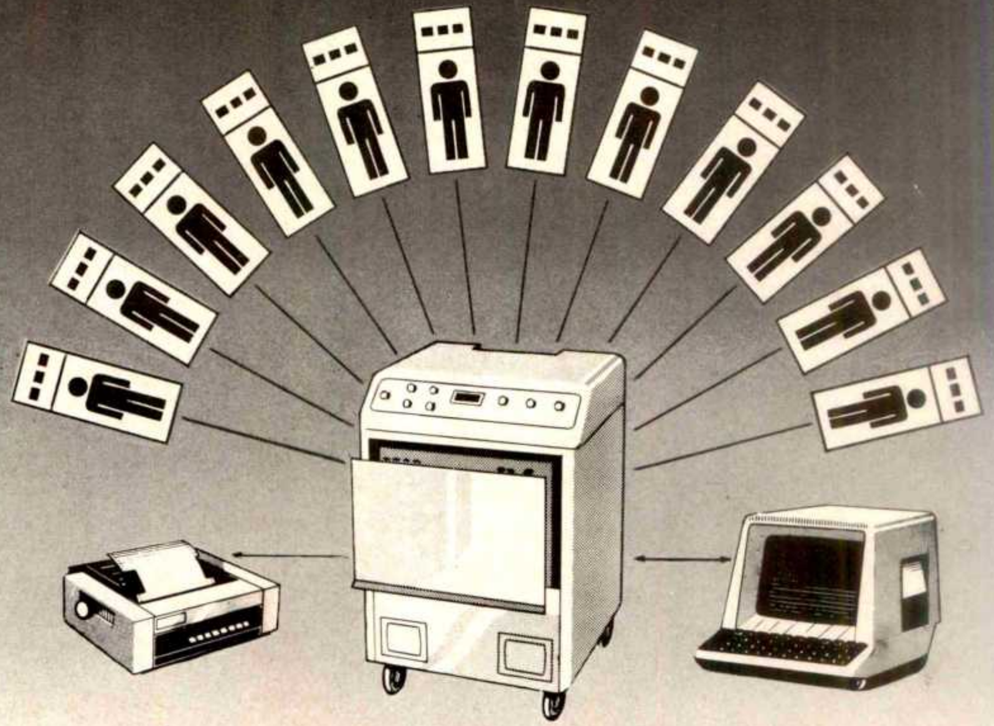

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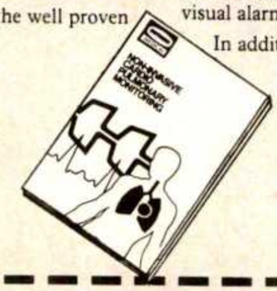

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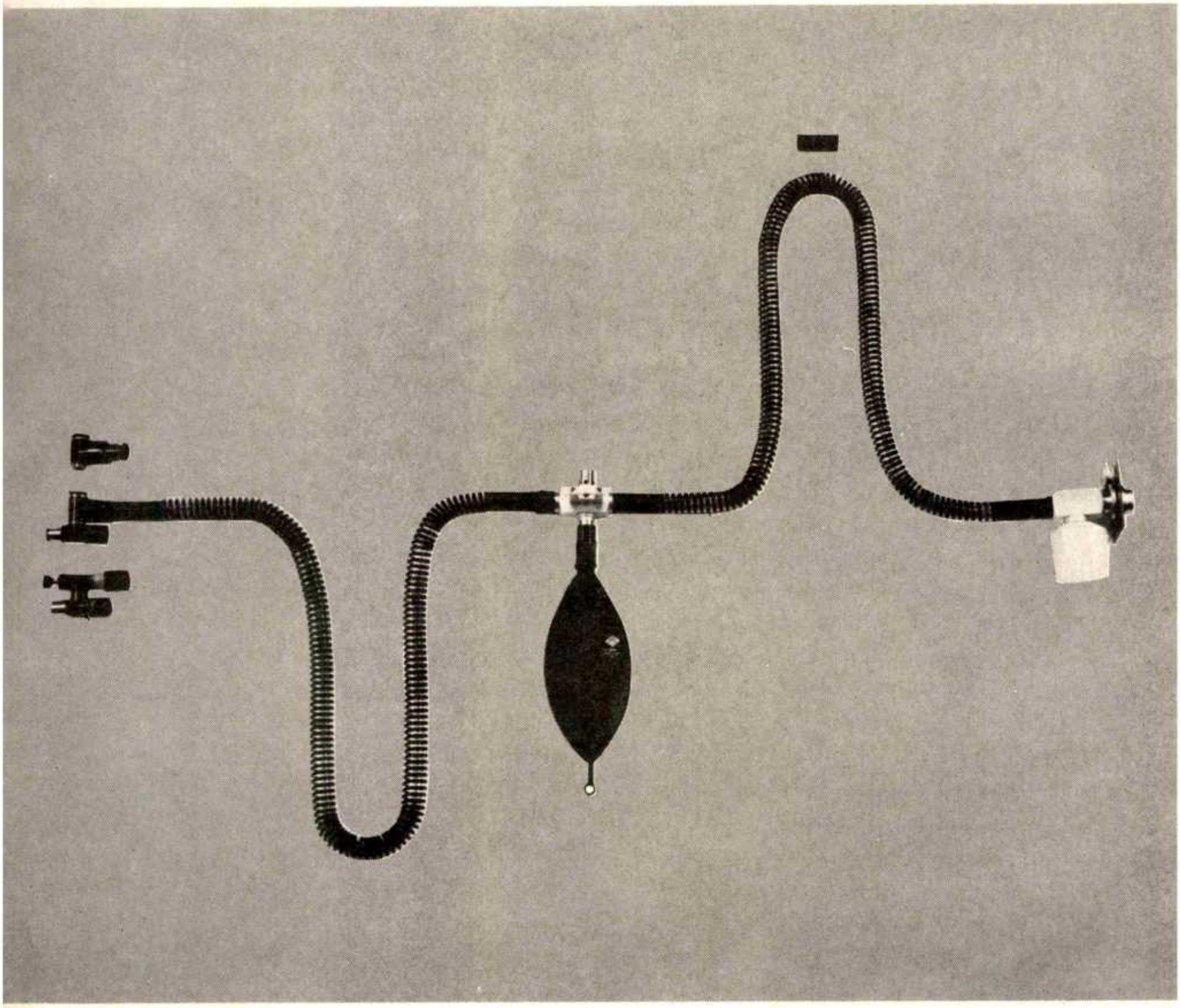

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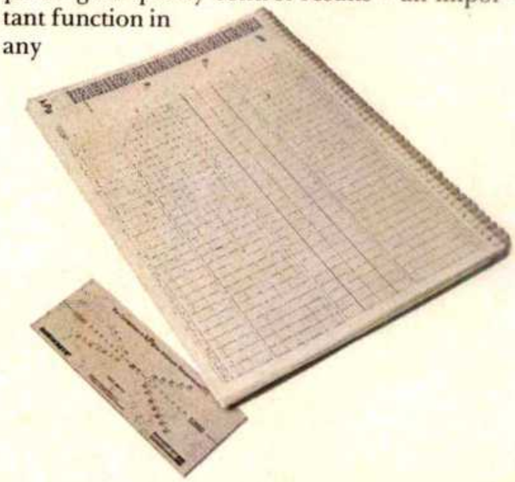

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EDITORIAL

NEUROMUSCULAR BLOCKING DRUGS

The introduction of drugs which block neuromuscular transmission was one of the major milestones of anaesthesia. In clinical use the drugs are remarkably safe provided that their users understand their actions and how these can be changed by disease and by other drugs, but they are not entirely without risk and Harrison (1978) has identified a fraction of anaesthetic deaths associated with their potential dangers. Drs Ronald Miller and Katz recently organized a meeting in San Francisco of interested workers who reviewed the present and future use of neuromuscular blocking drugs. Amongst many topics discussed were the mode of action of the drugs, the use of compartmental models to relate drug administration to effect, possible new agents and the assessment of the actions of the drugs in man.

Mode of action. The transmission of an impulse from the nerve to the muscle is complex and there are many sites at which drugs can act. Tubocurarine and suxamethonium act partly by combination with the acetylcholine receptors on the postsynaptic membrane, but there is convincing evidence that they also have actions on similar receptors in the prejunctional nerve terminal (Standaert, 1964; Standaert and Adams, 1965; Riker and Okamoto, 1969). The presynaptic action of tubocurarine is involved in the marked fade of a tetanic contraction seen when it is used. Normally the acetylcholine (ACh) released by the nerve terminal acts both post- and prejunctionally. The prejunctional effect facilitates release of more quanta of transmitter at the next impulse. Block of the prejunctional receptors by tubocurarine leads to succeeding stimuli releasing less ACh and hence the fade.

Standaert and his colleagues (1976) are now proposing another part of the transmission mechanism which is susceptible to drugs. They suggest that cyclic adenosine monophosphate (cAMP) may be the link between the nerve action potential and the entry of calcium into the nerve terminals which spectacularly increases the rate of release of ACh. The suggestion is that the nerve action potential activates adenylate cyclase in the nerve terminal membrane which converts ATP to cAMP. This acts on a protein kinase which opens the calcium channel. The cAMP is degraded to adenosine monophosphate by a phosphodiesterase. This hypothesis predicted that the following drugs would modify neuromuscular transmission. Adenylate cyclase activators such as sodium fluoride and prostaglandin E_1 should increase transmission, as should the use of diffusible analogue of cAMP—dibutyryl cAMP. Inhibitors such as alloxan would cause block and also reduce the effects of activators, but not that of dibutyryl cAMP. Phosphodiesterase inhibitors such as theophylline should increase transmission, whereas activation by imidazole should produce block. Finally adenosine, which inhibits protein kinases, and verapamil, which blocks calcium channels, should also cause a block. All these predicted effects were demonstrable. In man, azathriopine has been shown to antagonize the block produced by tubocurarine; it has phosphodiesterase inhibiting effects (Dretchen et al., 1976). Frusemide may also cause problems. Standaert reported that in low doses its protein kinase inhibiting action led it to potentiate the block produced by tubocurarine, whereas in high doses ($1\ \mathrm{mg\ kg^{-1}}$) it antagonizes the block—perhaps because it was inhibiting phosphodiesterase. Are these effects clinically significant?

The effects of antibiotics on neuromuscular transmission have been studied by Singh, Harvey and Marshall (1978). The aminoglycosides produce a block similar to that seen with high concentrations of magnesium. Their effects may be reversed by increasing the calcium concentration and, partially, by neostigmine. Polymyxins are more potent blockers and their effects are not antagonized by neostigmine, and only by calcium if it is given early. These drugs also have local anaesthetic properties, but whether that action produces the block is as yet undetermined.

Compartmental models. Many anaesthetists use neuromuscular blocking drugs by giving bolus i.v. doses of varying size and at varying intervals. The subsequent fate of the drug and its course of action can be modelled fairly satisfactorily by assuming the body to be composed of two (or three) compartments into and out of which the drugs flow down concentration gradients. During recovery there is a good correlation between the plasma concentrations of the drugs and their effects as determined by the responses to nerve stimulation. Greenblatt and Koch-Weser (1975) and Hull (1979) discuss the principles of model theory.

Perhaps the most useful characteristics of the two-compartment model are the rate constants, or half-lives describing the first "distribution" phase and the second "elimination" phase and the apparent volumes of two compartments. These values have been derived for pancuronium (McLeod, Watson and Rawlins, 1976) and tubocurarine (Miller et al., 1977). Both papers compare results in patients with normal and impaired renal function. Renal failure slows the elimination for both drugs, but more so for pancuronium. The effects on the compartment volumes were less significant. Somogyi, Shanks and Triggs (1977) reported a study of patients with obstructive jaundice who were given pancuronium. The final elimination phase was greatly prolonged. At the San Francisco meeting Du Valdestin from Paris reported similar results in patients with obstructive jaundice and also that patients with cirrhosis showed not only a prolonged elimination for pancuronium, but also an increased volume of distribution. The significance for the clinical use of the drugs is that patients with renal failure or obstructive jaundice may need the same initial dose as the normal patients, but that repeated doses will only be necessary at intervals much longer than customary. The patient with cirrhosis may need a larger initial dose, but the need for increments will occur at longer intervals.

A future generation of neuromuscular blockers? Many anaesthetists might feel that already we have enough agents—and problems. Others do not, and point out that although suxamethonium is the only agent with a significant rapid onset it does have some dangers. The most significant is its role as a trigger for malignant hyperthermia, for its other effects can be minimized with care. Similarly, many of the competitive blockers have other actions such as ganglion block, cardiac vagal block and histamine release. Agents free from these effects ("clean" in the current jargon) would be useful. One such drug is now in use in the United States. Metocurine (dimethyl tubocurarine) is free of the cardiovascular effects (Hughes, Ingrams and Payne, 1976; Savarese, Ali and Antonio, 1977). Its onset is similar to that of tubocurarine and it is between tubocurarine and pancuronium in potency.

The goal of a competitive drug with an onset of action as rapid as suxamethonium is not so easily reached. Kitz and Savarese in Boston have explored a series of quaternary compounds containing ester links which will be hydrolysed rapidly by plasma cholinesterase. At least one drug is to undergo clinical trial this year. Presumably its short action will be lengthened in patients with atypical or absent cholinesterase. However, its action may be antagonized by anticholinesterases. An alternative approach to finding the rapid onset and recovery has been to modify the pancuronium molecule. One such compound—dacuronium—did not live up to expectation (Norman and Katz, 1971). Another derivative is known only by its code number (NC45), but shows more promise. Initial clinical trials were reported by Crul and Agoston at the meeting. Its action is rapid in onset, recovery is faster than that of tubocurarine and it appears not to be cumulative. Its cardiovascular actions appear minimal.

One new antagonist may also have some clinical value. 4-Aminopyridine both prolongs the action potential and facilitates the entry of calcium into nerve terminals. Hence it acts presynaptically to increase the amount of ACh released. It can antagonize neuromuscular block produced by competitive drugs, by depolarizing agents in Phase II, by antibiotics and by botulinus toxin. Unfortunately, in doses needed clinically, it crosses the blood–brain barrier and may produce convulsions. However, smaller doses greatly reduce the amount of neostigmine needed to antagonize competitive block and the mixture may help in those situations where the paralysis is produced by a mixture of effects (Booij, Miller and Crul, 1978).

Testing new drugs and monitoring neuromuscular blockade. One plea made at the meeting was that those who investigate the effects of drugs at the neuromuscular junction should use a common experimental technique. Ulnar nerve stimulation and recording the effect on the contraction of the adductor pollicis are becoming standard methods in man, but the choice of the frequency of stimulation is critical; rates of greater than 0.1–0.15 Hz can lead to an intensification of the block (Ali, Utting and Gray, 1970). The occasional tetanic rate of stimulation will alter the responses. Other factors may include the use of potent inhalation anaesthetics and alterations in acid–base balance. Whilst it is unlikely that a standard technique can be agreed, it is essential that investigators must report the conditions of their studies fully and know the limitations of their recording methods. Dr Ronald Katz of Los Angeles is co-ordinating an attempt at a common technique: those interested should discuss it with him.

Why do anaesthetists rarely use nerve stimulators to monitor neuromuscular blockade? The variability of individual response, together with the effects of neurological, renal and hepatic disease, must lead to situations in which patients are either partially paralysed at the end of an anaesthetic despite the use of anticholinesterase drugs, or in which the anticholinesterases are ineffective. Many of the American speakers favour the technique of monitoring and titrating the dose of relaxant to match the exact need. Those in the United Kingdom may feel they do not have the time to wait; for it may take up to 6 minutes or more for the effects to reach their maximum and the pressures of lists with many cases do not allow this time. Nevertheless, with prolonged surgery in the presence of possible renal or hepatic dysfunction it is sensible to use a stimulator to monitor the progress of the block. Interpretation of the findings will be helped if the anaesthetist is familiar with the responses in normal patients. When normal transmission is not present at the end of the operation artificial ventilation must continue until the cause is found and dealt with.

The San Francisco meeting was both interesting and useful in defining what we know and can expect in the clinical use of neuromuscular blocking drugs. The organizers and the chairmen—Drs Miller and Katz are to be congratulated.

John Norman

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AIRWAY CLOSURE AND FLUID FILTRATION IN THE LUNG

N. SMITH-ERICHSEN AND G. BØ

SUMMARY

We have investigated the effect of airway closure on fluid balance in the isolated, perfused rabbit lung in which the alveolar, pleural and vascular pressures could be regulated independently. The rate of filtration into the interstitial space was monitored by continuous weighing. A reduction in pleural pressure of 0.5 kPa with open airways increased fluid filtration by 0.11 g min^{-1}. Reduction in pleural pressure of 0.5 kPa with the main airways closed reduced the alveolar pressure by 0.4 kPa and increased fluid filtration by 0.86 g min^{-1}. We concluded that the pleural pressure is transmitted poorly to the alveolar interstitial space in the normal lung with open airways. However, airway closure allows the pleural pressure to be transmitted almost completely to this interstitium, with interstitial oedema as a possible consequence.

Prominent features of post-traumatic pulmonary insufficiency include narrowing and collapse of small airways and the development of interstitial oedema (Sladen, Laver and Pontoppidan, 1968). This has led some authors to call the condition "wet lung" or "congestive atelectasis" (Schramel et al., 1968). Many clinicians accept that abnormal accumulation of fluid in the lungs causes this condition and diuretics are used in the treatment of post-traumatic pulmonary insufficiency as a matter of routine.

Much attention has been paid to the role of the vascular tree in post-traumatic pulmonary insufficiency (Blaisdell and Scholobohm, 1973), but less to the airways and the possibility that there may be a relationship between collapse of small airways and the accumulation of fluid in the lung interstitium. As a consequence of collapse of small airways, the intrathoracic pressure becomes more negative not only in the pleural space, but also in the pulmonary interstitium. It is likely that a more negative interstitial fluid pressure increases the hydrostatic pressure gradient across the capillary wall, causing efflux of water into the pulmonary interstitial space (Pontoppidan, Laver and Geffin, 1970), although there are no experimental data to support this view. Clinical reports of severe pulmonary oedema associated with upper airway obstruction support the view that collapse of airways may cause oedema (Schaer and Roth, 1977). The purpose of the present study was to examine the role of airway closure in inducing pulmonary oedema.

METHODS

Rabbits of either sex (weight 3–6 kg) were anaesthetized with phenobarbitone 30–50 mg kg^{-1}. A tracheotomy was performed and the lungs were ventilated artificially. Pancuronium bromide 1–1.5 mg was given for muscle relaxation. The chest was opened by median sternotomy and the heart and lungs removed with as little trauma as possible. Heparin 5000 units was given before removal of the organs. A catheter was placed in the pulmonary artery through an incision in the right ventricle and a second catheter in to the left atrium through its appendix. Care was taken to avoid air embolism to the lungs during the procedure. A tight ligature was placed around both ventricles.

The preparation was placed in an air-tight Perspex chamber at a temperature of 37 °C and connected to a balanced force transducer (Statham) for continuous monitoring of the weight of the preparation. The weight changes were recorded with a Hewlett-Packard recorder.

The vascular catheters were connected to a constant pressure perfusion system outside the chamber to maintain constant microvascular pressures in the preparation. The temperature of the perfusate was maintained at 37 °C. Flow through the lungs was recorded continuously using a Nycotron electromagnetic flowmeter placed in the arterial line.

The trachea was connected to a ventilator (Ideal Respiration Pump, C. F. Palmer, London) outside

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the chamber via tubing inserted through the chamber wall (fig. 1).

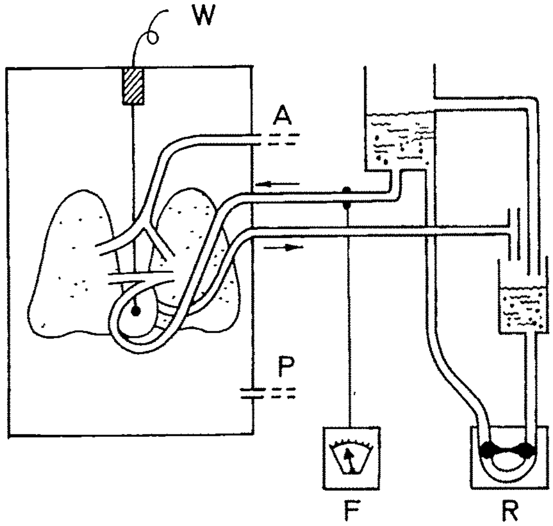

FIG. 1. The experimental preparation with Perspex chamber and the constant pressure perfusion system. A = the main airway and its connection to the respirator or ambient air; P = suction system controlling the chamber pressure (pleural pressure); R = roller pump; F = record of arterial flow; W = weight recording system.

A 5% solution of dextran 70 (Macrodex, Pharmacia) (1500 ml) with physiological concentrations of sodium, potassium, calcium, chloride, bicarbonate and glucose, heparin 5000 units and papaverine 10 mg (to minimize changes in vascular tone) was used as perfusate. By the use of a perfusate volume of approximately 1.5 litre, colloid osmotic pressure was maintained constant during the perfusion. Carbon dioxide 5% in oxygen was bubbled through the perfusate to maintain normal pH. The same gas was used for ventilation of the lungs at the beginning of the perfusion to avoid absorption of trapped gas. This prevented reduction in lung gas volume and thereby also slow changes in lung blood volume.

The air-tight Perspex chamber was connected to a suction system which allowed the air pressure within the chamber to be changed. Thus we could change the pressure on the lung surface (pleural pressure) independently of vascular and airway pressures. The time without perfusion and ventilation of the preparation was about 15 min. The positive pressure ventilation and perfusion were started at the same time. The vascular pressures were adjusted to produce a flow of between 50 and 150 ml min^{-1} and to ensure a stable weight of the preparation during ventilation. After 10–15 min ventilation was stopped and the vascular pressures increased to a value which caused a slow and constant gain in lung weight of between 0.3 and 0.5 g min^{-1}. This weight gain was assumed to reflect accumulation of fluid in the lung interstitium as a result of filtration from the capillaries (Lunde and Waaler, 1969). The slope of the recorder line was taken as the fluid filtration rate (FFR). FFR 0.3–0.5 g min^{-1} was obtained with a mean pulmonary artery pressure of about 1.5 kPa and a left atrial pressure of 0.3–0.7 kPa. The left atrial pressure was always adjusted to a value greater than alveolar pressure to ensure that the lung preparation was of "zone III" type ($P_{PA} > P_{LA} > P_A$) (West, Dollery and Naimark, 1964). After this adjustment the vascular pressures were maintained constant throughout the rest of the experiment.

The chamber pressure (pleural pressure, P_{pl}) was then varied between -0.5 and -1.0 kPa and kept at each value for at least 2 min to obtain changes in FFR. At first this was performed with a constant ambient tracheal pressure (open airways) causing an increase in transpulmonary pressure from 0.5 to 1.0 kPa and thereby an increase in lung gas volume. Then the trachea was closed just above the carina with a "flow-directed pulmonary artery balloon catheter" at P_{pl} of -0.5 kPa. The distal lumen of the catheter was connected to a U-tube manometer to measure airway pressure distal to the occlusion. Then P_{pl} was varied again from -0.5 to -1.0 kPa and kept at each value for at least 2 min to obtain FFR (closed airways).

Finally, the trachea was re-opened by deflating the ballon catheter and the same tests were repeated with open airways.

RESULTS

Any change in vascular pressures of the preparation, either inflow (arterial) or outflow (left atrial), and any change in airway or chamber pressure (pleural pressure, P_{pl}) produced a change in lung weight. There was an early, rapid phase (within 1 min) caused mainly by changes in pulmonary blood volume (perfusate volume). After the 1st min another less steep, but straight, line was obtained reflecting fluid accumulation only (Lunde and Waaler, 1969). The slope of this linear part is an expression of FFR. Figure 2 shows the effect on the weight recorder of a separate increase in vascular pressure (from A to B) and a separate reduction in chamber pressure (from

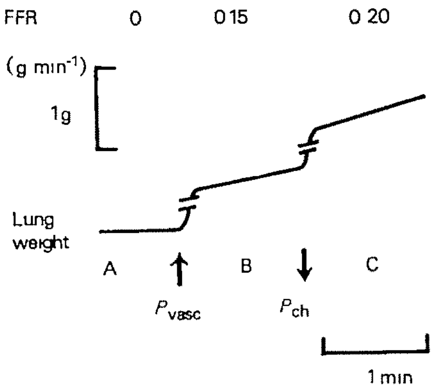

FIG. 2. The effects on lung weight of a separate increase in vascular pressure (P_{vasc}) (from A to B) and a separate reduction in chamber (pleural) pressure (P_{ch}) (from B to C). Both manœuvres caused increases in the fluid filtration rate (FFR).

B to C). The steep parts of the curve from A to B and B to C reflect increases in pulmonary blood volume. The straight and less steep parts (A, B, C) reflect fluid filtration only.

Table I shows FFR in five pairs of lungs with open and closed airways and after the re-opening of the airways. When P_{pl} was changed from -0.5 to -1.0 kPa and *vice versa* with open airways, a mean change in FFR of 0.11 g min^{-1} occurred (range 0.05–0.25 g min^{-1}) (fig. 3). With closed airways, the same variation in P_{pl}, from -0.5 to -1.0 kPa, caused a mean change in FFR of 0.86 g min^{-1} (range 0.35–1.2 g min^{-1}) (fig. 4). Simultaneously, the airway pressure distal to the occlusion—and thereby also the alveolar pressure—was reduced by 0.4 kPa. The filtration tests performed after re-opening the trachea showed larger changes in FFR with a mean value of 0.31 g min^{-1} (range 0.15–0.45 g min^{-1}) compared with the tests performed before the occlusion manœuvre.

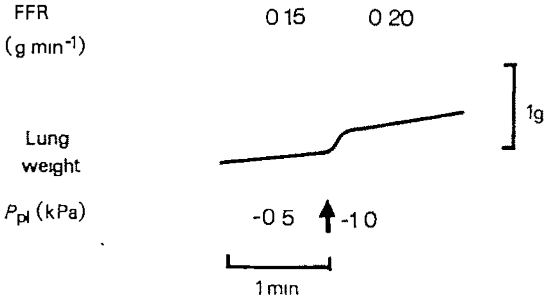

FIG. 3. Effect on fluid filtration rate (FFR) of a stepwise reduction in chamber pressure (pleural pressure, P_{pl}) from -0.5 to -1.0 kPa under conditions of open airways.

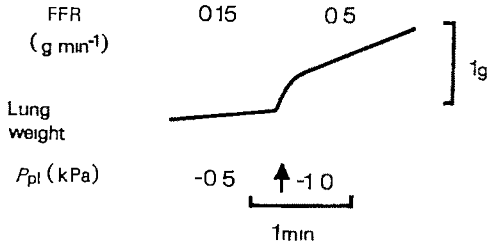

FIG. 4. The effect on FFR of a stepwise reduction in chamber pressure (P_{pl}) from -0.5 to -1.0 kPa with the airways closed.

For technical reasons we preferred to study the process of a slow and continuous outward filtration of fluid into the pulmonary interstitium. However, we observed that with no filtration or even an inward fluid filtration, a change to outward fluid filtration could be produced merely by a reduction of the pleural pressure with open or closed airways.

DISCUSSION

In this study we have found that a normal negative pressure inspiration (reduction in pleural pressure by 0.5 kPa) against a closed trachea increased FFR by

TABLE I. *Effects on fluid filtration rate (FFR) (g min^{-1}) of changes in chamber ("pleural") pressure of 0.5 kPa under conditions of open and closed airways in five pairs of lungs*

	Chamber pressure (kPa)									
	No. 1		No. 2		No. 3		No. 4		No. 5	
	−0.5	−1.0	−0.5	−1.0	−0.5	−1.0	−0.5	−1.0	−0.5	−1.0
Open airways	0.45	0.50	0.50	0.60	0.15	0.20	0.65	0.90	0.45	0.55
Closed airways	0.40	1.60	0.35	1.20	0.15	0.50	0.60	1.40	0.25	1.35
Open airways	0.50	0.80	0.35	0.50	0.30	0.50	0.55	1.00	0.45	0.90

0.86 g min^{-1} whereas inspiration with open airways increased FFR by only 0.11 g min^{-1}. We suggest that multiple small airway occlusions would produce similar changes.

Transvascular fluid filtration across the pulmonary microvascular wall depends on the hydrostatic pressure gradient, the colloid osmotic pressure, the permeability of the vessel wall and the microvascular surface area (Staub, 1974). The use of a relatively large perfusate volume prevents changes in colloid osmotic pressure from playing a role. The constant inflow and outflow pressures during the perfusion ensured constant microvascular pressure (Bø, Hauge and Nicolaysen, 1977). Transient reversible changes in FFR exclude changes in permeability. Changes in microvascular surface area as a cause of changes in FFR are also unlikely because the lung preparation was a zone III type (West, Dollery and Naimark, 1964) throughout the perfusion and papaverine was added to the perfusate to minimize changes in vascular tone. The observation that a separate change in pleural pressure can change the direction of fluid filtration cannot be explained by assuming a change in capillary surface area as this would change only the amount of filtration but not the direction. However, we cannot completely exclude small changes in capillary surface area as a factor in the changes in filtration. Thus, by exclusion we deduce that change in pulmonary interstitial fluid pressure is the major cause of changes in FFR.

The lung interstitium can be subdivided into two compartments, the alveolar interstitium and the extra-alveolar interstitium located in the perivascular and peribronchial space (Permutt et al., 1961; Permutt, 1965). As a result of the geometry of the lung, the interstitial fluid pressure in this extra-alveolar space may be more negative than the pleural pressure itself by a normal negative pressure inspiration with open alveoli, whereas the alveolar interstitial fluid pressure is not affected at all (Permutt, 1965; Meyer, Meyer and Guyton, 1968; Hughes, 1971). Other workers have suggested that considerable fluid filtration may occur directly through pre-capillary vessels (Whayne, Thomas and Severinghaus, 1968; Iliff, 1971). If we assume that these pre-capillary vessels are located in the extra-alveolar space, fluid filtration through these vessels must be increased by inspiration. An increase in lung gas volume increases the volume of the limited and closed extra-alveolar space resulting in a reduction of the interstitial fluid pressure of this compartment. This mechanism may be responsible for the change in FFR of 0.11 g min^{-1}, which was found after inflation of the lungs with open airways. Another more reasonable explanation of this increase in FFR could be operative trauma to the lung tissue with permanent airway collapse in some regions. Airway collapse produces more negative alveolar interstitial fluid pressure irrespective of whether the closure is located centrally or peripherally. Therefore we may conclude that the negative pleural pressure is poorly or not transmitted to the alveolar interstitium in normal lungs with open airways. The intrathoracic pressure may therefore affect the pulmonary fluid balance only through its effect on the pulmonary inflow and outflow vascular pressures.

The airway occlusion tests were designed to simulate a situation of airways closure and alveolar collapse. Breathing efforts under such circumstances may cause peaks of marked negative pleural/intrathoracic pressure. Airway closure allows the negative pleural pressure to be transmitted almost completely to the alveoli beyond the point of closure. Such reductions in alveolar and thereby alveolar interstitial fluid pressure explain the marked increase in FFR (table I).

An unexpected finding was a greater change in FFR (0.33 g min^{-1}) after the occlusion experiments compared with before (0.11 g min^{-1}), although the airways were open in both instances. The occlusion manœuvre, with an increased efflux of water, may have caused widespread and permanent collapse of small peripheral and easily collapsible airways.

We conclude that changes in pleural and intrathoracic pressure are not, or are only poorly, transmitted to the alveolar interstitium in the normal lung with open airways under static conditions with zero air flow. However, it is transmitted almost completely to this interstitium in areas with closed airways. The interstitial fluid pressure is probably similar to the alveolar pressure in the alveolar interstitium in the normal lung with open airways. However, in areas of lung where airways are not patent, the alveolar interstitial fluid pressure may be closer to the negative pleural pressure. We suggest that this mechanism partly explains the "wet lung" state of post-traumatic pulmonary insufficiency.

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FERMETURE DES PASSAGES D'AIR ET FILTRATION FLUIDE DANS LES POUMONS

RESUME

Nous avons fait des recherches sur l'effet de la fermeture des passages d'air sur l'équilibre hydrique d'un poumon isolé et irrigué d'un lapin, sur lequel les pressions alvéolaires, pleurales et vasculaires pouvaient être réglées indépendemment. Le taux de filtration dans l'espace interstitiel a été surveillé par un pesage continu. La réduction de la pression pleurale de 0,5 kPa, avec les passages d'air ouverts, a augmenté la filtration fluide de 0,11 g min^{-1}. La réduction de la pression pleurale de 0,5 kPa, avec les principaux passages d'air fermés, a réduit la pression alvéolaire de 0,4 kPa et augmenté la filtration fluide de 0,86 g min^{-1}. Nous en avons conclu que la pression pleurale est mal transmise à l'espace interstitiel alvéolaire dans le poumon normal lorsque les passages d'air sont ouverts. La fermeture des passages d'air permet cependant à la pression pleurale d'être transmise presque entièrement à cet interstice, l'oedème interstitiel en étant une des conséquences possibles.

LUFTWEGVERSCHLUSS UND FLÜSSIGKEITSFILTRIERUNG IN DER LUNGE

ZUSAMMENFASSUNG

Wir haben die Wirkung eines Luftwegverschlusses auf das Flüssigkeitsgleichgewicht in der isolierten, durchströmten Hasenlunge untersucht, in der der Alveolen-, Pleura- und Gefässdruck unabhängig von einander geregelt werden konnte. Die Filtrierungsrate in den Interstitialstreifen wurde durch kontinuierliches Wiegen überwacht. Ein Druckabfall von 0,5 kPa in der Pleura bei offenen Luftwegen steigerte die Flüssigkeitsfiltrierungsrate um 0,11 g min^{-1}. Ein Abfall von 0,5 kPa im Pleuradruck bei verschlossenem Hauptluftweg verringerte den Alveolendruck um 0,4 kPa und steigerte die Flüssigkeitsfiltrierung um 0,86 g min^{-1}. Wir folgerten daraus, dass in der normalen Lunge mit offenen Luftwegen der Pleuradruck unzureichend zum alveolaren Interstitialstreifen übertragen wird. Luftwegverschluss gestattet jedoch eine beinahe vollständige Übertragung des Pleuradruckes zu diesem Interstitium, mit der möglichen Folge eines Interstitialödems.

CIERRE DE LAS VIAS RESPIRATORIAS Y FILTRACION DE FLUIDOS EN EL PULMON

SUMARIO

Hemos averiguado el efecto del cierre de las vías respiratorias sobre el balance de los fluídos en el pulmón aislado perfusado de un conejo en el cual las presiones alveolar, pleural y vascular podían regularse independientemente. El ritmo de filtración dentro del espacio intersticial se controlaba mediante mediciones de peso constantes. Al reducir la presión pleural en un 0,5 kPa y estando las vías respiratorias abiertas, se producía un aumento de la filtración de los fluídos de 0,11 g min^{-1}. Al disminuir la presión pleural en un 0,5 kPa y estando las vías respiratorias cerradas, la presión alveolar se reducía en un 0,4 kPa y se incrementaba la filtración de fluídos en un 0,86 g min^{-1}. Llegamos a la conclusión de que la presión pleural se transmite mal al espacio intersticial alveolar en el pulmón normal, cuando están abiertas las vías respiratorias. Sin embargo, el cierre de las vías respiratorias permita a la presión pleural transmitirse a dicho intersticio casi totalmente, lo que tiene por consecuencia posible un edema intersticial.

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PHARMACOKINETIC AND CLINICAL PHARMACOLOGICAL STUDIES WITH MEPIVACAINE AND PRILOCAINE

G. R. ARTHUR, D. H. T. SCOTT, R. N. BOYES AND D. B. SCOTT

SUMMARY

The tolerance and pharmacokinetic properties of mepivacaine and prilocaine were compared following i.v. infusion of 250 mg (0.88 and 0.97 mmol respectively) of each drug in five healthy volunteers. Side-effects were minor and occurred in only two subjects during the infusion of mepivacaine. Plasma concentrations of mepivacaine were greater in each subject than the corresponding values for prilocaine. The elimination half-life of mepivacaine was generally longer than that for prilocaine, whereas the total body clearance of prilocaine was consistently greater than the corresponding value for mepivacaine. For each subject the clearance of prilocaine substantially exceeded normal heptic blood flow and therefore an extra-hepatic site of metabolism of prilocaine has been postulated.

Many studies have been carried out, in both patients and volunteers, in which the detailed pharmacokinetics of certain local anaesthetic agents have been measured and attempts have been made to associate blood or plasma concentrations with pharmacological effects of these drugs (Boyes et al., 1971; Reynolds, 1971b; Scott, 1975). Although early clinical studies suggested smaller blood concentrations and a more rapid clearance for prilocaine than for lignocaine, a more detailed evaluation of the pharmacokinetics of prilocaine has not been carried out in man. Although mepivacaine has been the subject of pharmacokinetic evaluation (Reynolds, 1971a; Tucker and Mather, 1975) there has been no systematic evaluation of the relationship between blood concentration of the drug and its toxic side-effects. This current study compared the pharmacokinetics and clinical effects of both prilocaine and mepivacaine following i.v. administration in a group of volunteers.

METHODS

The study was approved by the appropriate hospital ethics committee. After being informed in detail of the experiments, five healthy males (age 24–35 yr) consented to participate. On two occasions, separated by at least 7 days, each volunteer received, over 12.5 min, i.v. infusion of 250 mg of either mepivacaine HCl (0.88 mmol) or prilocaine HCl (0.97 mmol) in 50 ml saline. The experiment was carried out in a double-blind manner and the infusions were administered in a random sequence. Venous blood samples were taken during the infusion and at frequent intervals for 4 h thereafter. Systemic arterial pressure was monitored during the course of the experiment and the e.c.g. was tape-recorded continuously for 50 min starting 10 min before commencing the infusions.

The venous blood samples were collected into heparinized tubes, centrifuged, and the separated plasma stored in a freezer until analysis. Plasma concentrations (expressed as free base) of mepivacaine and prilocaine were determined using a gas chromatographic procedure similar to that described by Tucker (1970). Under the conditions employed the minimum detectable limit for both drugs was 0.05 $\mu g\ ml^{-1}$ and there was a coefficient of variation of $\pm 5\%$ at a concentration of 1 $\mu g\ ml^{-1}$.

The plasma concentrations of prilocaine and mepivacaine for each volunteer were subjected to manual "curve stripping" and the resulting mathematical constants were used for pharmacokinetic analysis (see Appendix). From these data the elimination half-life ($T_{\frac{1}{2}}$), area under the plasma drug concentration curve (AUC_c) and total body clearance ($\dot{V}$) of drug could be derived. The area under the plasma concentration curve was also measured geometrically (AUC_m) as a means of checking the pharmacokinetic calculations.

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TABLE I. *Pharmacokinetic data for mepivacaine after i.v. infusion in five volunteers. α is the slope of the rapid distribution phase of the drug; β is the slope of the slower elimination phase of the drug; A and B the intercept values of the α and β phases on the plasma drug concentration axis at time (t) = 0 (values corrected for infusion time—see Appendix, equations (2) and (3)); $T_{\frac{1}{2}}$ the elimination half-life of the drug; AUC_0 and AUC_m the calculated and measured areas under the plasma drug concentration curve (see Appendix); $\dot{V}$ the total body clearance of the drug from the body*

	Volunteer no.						
	1	2	3	4	5	Mean	SD
α (min^{-1})	0.136	0.169	0.128	0.074	0.100	0.101	(±0.066)
β (min^{-1})	0.0043	0.0084	0.0058	0.0045	0.0064	0.0059	(±0.0016)
A (μg ml^{-1})	3.6	3.04	2.80	1.28	6.66	3.48	(±1.98)
B (μg ml^{-1})	2.28	1.31	2.54	1.80	2.95	2.18	(±0.64)
$T_{\frac{1}{2}}$ (min)	162	83	120	154	108	125	(±32)
AUC$_0$ (μg ml^{-1} min^{-1})	559	175	463	417	526	428	(±152)
AUC$_m$ (μg ml^{-1} min^{-1})	579	180	469	444	530	440	(±155)
$\dot{V}$ (litre min^{-1})	0.45	1.43	0.54	0.60	0.48	0.70	(±0.41)

TABLE II. *Pharmacokinetic data of prilocaine after i.v. infusion in five volunteers*

	Volunteer no.						
	1	2	3	4	5	Mean	SD
α (min^{-1})	0.080	0.105	0.364	0.061	0.105	0.143	(±0.125)
β (min^{-1})	0.0052	0.0057	0.0107	0.146	0.0068	0.0086	(±0.0040)
A (μg ml^{-1})	1.48	1.24	8.29	1.13	2.17	2.86	(±3.06)
B (μg ml^{-1})	0.39	0.37	0.77	0.84	0.58	0.59	(±0.21)
$T_{\frac{1}{2}}$ (min)	134	122	65	43	102	93	(±38)
AUC$_0$ (μg ml^{-1} min^{-1})	94	77	95	76	106	90	(±13)
AUC$_m$ (μg ml^{-1} min^{-1})	97	74	114	71	94	90	(±18)
$\dot{V}$ (litre min^{-1})	2.66	3.25	2.64	3.29	2.36	2.84	(±0.41)

RESULTS

No significant alterations in arterial pressure or e.c.g. were observed during any of the infusions . The only subjective signs of toxicity were noted by two of the volunteers who reported numbness of the tongue and slight lightheadedness during the infusion of mepivacaine.

The plasma concentrations of prilocaine were substantially less than those of mepivacaine in all instances (fig. 1). The relevant pharmacokinetic data for each drug calculated from the plasma concentration data are summarized in tables I and II. The elimination half-life data for the two drugs suggested a more rapid decrease in plasma concentrations for prilocaine. There was considerable intersubject variability in these half-life data and, at least in subject 2, the rate of elimination of mepivacaine appeared to exceed the corresponding rate for prilocaine. However, the total body clearance of prilocaine was consistently greater than that of mepivacaine and,

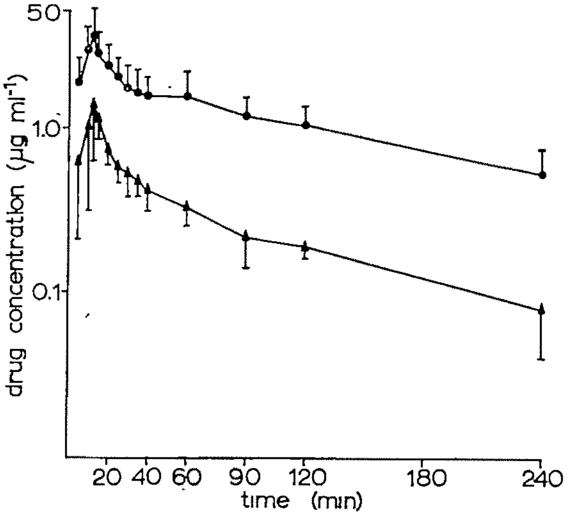

FIG. 1. Mean venous plasma concentrations of mepivacaine (●) and prilocaine (▲) after i.v. infusion of 250 mg of each drug, on separate occasions, in five male volunteers.

for each volunteer, the clearance value of prilocaine was in excess of 2 litre min^{-1}.

DISCUSSION

Local anaesthetic agents, in particular lignocaine and bupivacaine, have been subject to extensive pharmacokinetic evaluation. Attempts have been made to associate blood concentrations of these drugs with their pharmacological side-effects (Boyes et al., 1971; Reynolds, 1971b; Scott, 1975). Although early reports suggested that prilocaine was less toxic than other amide local anaesthetic agents and that plasma concentrations were substantially smaller when equal doses were administered, this drug has not been the subject of a detailed pharmacokinetic evaluation. The pharmacokinetics of mepivacaine has been reported previously in volunteers (Reynolds, 1971a; Tucker and Mather, 1975). It should be noted that the data for this drug shown in table I compare well with those reported previously by Tucker and Mather (1975). For example, they reported a mean terminal half-life of 114 min and a clearance of 0.78 litre min^{-1}, (in seven subjects) compared with the values of 125 min and 0.70 litre min^{-1} respectively in the present study.

The large clearance values for prilocaine shown in table II are of particular interest. Not only are these values approximately four times greater than those for mepivacaine but also they exceed 2 litre min^{-1} in each individual. Local anaesthetic drugs of the amide type are usually considered to be metabolized almost entirely by the liver. The mean value for hepatic blood flow in a normal population is often taken to be 1.7 litre min^{-1} (Price et al., 1960)—less than all the calculated clearance values for prilocaine in this study. This large plasma clearance of prilocaine may be explained by three possible mechanisms. First, all our volunteers may have had inordinately great hepatic blood flows. This explanation is unlikely because the clearance values for mepivacaine are very similar to those reported previously and if our volunteers were unusual their clearance values would have been greater. Second, AUC_0, which was used as the denominator in the clearance calculation (Appendix, equation 5), may have been underestimated because blood sampling was terminated at 240 min. Prilocaine taken up by tissues may have returned to the general circulation only very slowly. This is unlikely to be the complete explanation of the high calculated clearance because in every instance virtually no drug was detectable in the samples at 240 min. AUC occurring after the initial 240-min measurement period would have to equal 50–100% of the AUC during the first 4-h measurement period in order that the clearance values be calculated at values equal to or less than hepatic blood flow. Furthermore, there was no indication that the slope of the plasma concentration curve was reducing as might be expected if drug was being returned to the circulation from a storage site. Third, it is possible that prilocaine undergoes some degree of extra-hepatic metabolism. In an early pharmacological evaluation Åkerman and others (1966) reported that prilocaine could be metabolized by both lung and kidney slices from the guineapig. It has been reported that prilocaine metabolism is an anaerobic process not involving the oxidative enzymes of the liver (Geddes, 1965; Åkerman et al., 1966). It is possible that the enzymes responsible for this amide hydrolysis process are not located exclusively in the liver. Because the lungs receive the entire cardiac output, it is attractive to speculate on this organ as a possible site of extra-hepatic metabolism. It is necessary only to postulate a very low extraction and metabolism of the drug by lung tissue in order to account for clearance in excess of hepatic flow. Further detailed experiments in animals are necessary to elucidate the site and mechanism of this possible extra-hepatic metabolism. If the lung is involved, the clinical implications could be extensive. The possibility that the lung acts as a buffer between the site of injection and the systemic circulation, thereby reducing the toxicity of certain local anaesthetic drugs, would be a specific example.

It is also noteworthy that in these experiments there was little or no objective or subjective sign of toxicity observed in any of the volunteers. This might be expected with prilocaine. However, previous reports have implied that the toxicity of mepivacaine was comparable to that of lignocaine. If compared with a previous study (Scott, 1975) in which lignocaine was administered under similar conditions to a group of volunteers (including four of the five subjects in the present study), the current data would suggest that, when administered i.v., mepivacaine may be less toxic than lignocaine and that larger plasma concentrations may be tolerated before side-effects are observed. However, it should be noted that, as previously reported by Tucker and Mather (1975), the clearance of mepivacaine is less than that for lignocaine. Therefore, there will be a greater tendency for mepivacaine to accumulate following multiple injections, as might occur in obstetric analgesia.

There are certain circumstances in clinical practice in which high doses of local anaesthetic drug must be given to ensure success. In addition, certain techniques involve injecting the drug i.v., for example Bier's block. In such instances prilocaine would appear to offer important advantages in terms of toxicity. The drug is frequently rejected because it can cause methaemoglobinaemia, but the consequences of this are seldom of clinical importance and this disadvantage is considerably outweighed by the advantage of reduced central toxicity.

APPENDIX

Pharmacokinetic analysis

The plasma concentration–time relationships, after stopping the i.v. infusion, for both prilocaine and mepivacaine were analysed using equation (1):

$$C_1 = A^1e^{-\alpha t}+B^1e^{-\beta t} \qquad (1)$$

where C_1 = plasma concentration of the drug, α = the slope of the rapid distribution phase of the drug, β = the slope of the slower elimination phase of the drug, and A^1 and B^1 are the intercept values of the α and β phases on the plasma drug concentration axis at time (t) = 0.

The values of A^1 and B^1 were corrected for the infusion time using equations (2) and (3) (Loo and Riegelman, 1970):

$$A = \frac{\alpha\tau}{1-e^{-\alpha\tau}}.A^1 \qquad (2)$$

$$B = \frac{\beta\tau}{1-e^{-\beta\tau}}.B^1 \qquad (3)$$

where τ = the infusion time and A and B are the corrected intercept values.

The area under the plasma concentration curve (AUC) was measured ($\mathrm{AUC_m}$) using the trapezoidal rule and a correction for infinite time (Gibaldi, 1977).

AUC was also calculated ($\mathrm{AUC_c}$) from the relationship:

$$\mathrm{AUC_c} = \frac{A}{\alpha}+\frac{B}{\beta} \qquad (4)$$

$\mathrm{AUC_c}$ was used to estimate the total body clearance of each drug from the following equation (Gibaldi, 1977):

$$\text{Total clearance } (\dot{V}) = \frac{F.\mathrm{dose}}{\mathrm{AUC_c}} \qquad (5)$$

Normally, it is assumed that F (the fraction of the drug reaching the systemic circulation) equals 1 when drugs are administered i.v.

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PHARMACOCINETIQUE ET ETUDES CLINQUES PHARMACOLOGIQUES DE LA MEPIVACAINE ET DE LA PRILOCAINE

RESUME

On a comparé la tolérance et les propriétés pharmacocinétiques de la mépivacaine et de la prilocaine, après infusion intraveineuse de 250 mg (0,88 et 0,97 mmol respectivement) de chacun de ces médicaments à cinq volontaires en bonne santé. Les effects secondaires ont été mineurs et ne se sont manifestés que sur deux sujets pendant l'infusion de mépivacaine. Les concentrations de mépivacaine dans le plasma ont été plus importantes, sur chaque sujet, que les valeurs correspondantes pour la prilocaine. La demi-vie d'élimination de la mépivacaine a en général été plus longue que celle applicable à la prilocaine, alors que le coefficient d'épuration plasmatique total du corps, applicable à la prilocaine, a été constamment plus important que le valeur correspondante applicable à la mépivacaine. Pour chaque sujet, le coefficient d'épuration plasmatique de la prilocaine a dépassé d'une manière substantielle le débit sanguin hépatique normal et on a donc postulé un site autre que la région hépatique pour le métabolisme de la prilocaine.

PHARMAKOKINETISCHE UND KLINISCH-PHARMAKOLOGISCHE UNTERSUCHUNGEN MIT MEDIVACAIN UND PRILOCAIN

ZUSAMMENFASSUNG

Nach intravenöser Infusion von 250 mg (0,88 bzw. 0,97 nmol), Mepivacain und Prilocain in fünf gesunde freiwillige Versuchspersonen wurden die Toleranz und pharmakokinetischen Eigenschaften der beiden Drogen verglichen. Nebenwirkungen waren geringfügig und kamen nur bei zwei Versuchspersonen während der Mepivacaininfusion vor. Die Plasmakonzentrationen von Mepivacain waren in allen Versuchspersonen grosser als die entsprechenden Werte für Prilocain. Der Eliminationshalbwert war

allgemein grösser für Mepivacain, als für Prilocain, wohingegen die Gesamt-Prilocainclearance des Körpers konsistent höher lag, als der entsprechende Wert für Mepivacain. Bei jeder Versuchsperson überschritt die Prilocainclearance wesentlich den normalen hepatischen Blutstrom und es wurde daher ein extra-hepatischer Situs für den Prilocainstoffwechsel postuliert.

ESTUDIOS FARMACOCINETICOS Y FARMACOLOGICOS CLINICOS CON MEPIVACAINA Y PRILOCAINA

SUMARIO

La tolerancia y las propiedades farmacocinéticas de la mepivacaina y de la prilocaina fueron comparadas tras la infusión intravenosa de 250 mg (0,88 y 0,97 mmol, respectivamente) de cada droga en cinco voluntarios sanos. Los efectos colaterales fueron menores y sólo se presentaron en dos sujetos durante la infusión de mepivacaina. Las concentraciones de plasma de mepivacaina eran mayores en cada sujeto para con los valores correspondientes de la prilocaina. El período de vida media de eliminación de la mepivacaina era mayor, en general, que el de la prilocaina, mientras que la depuración total de prilocaina en el cuerpo era permanentemente mayor que el valor correspondiente de la mepivacaina. Para cada sujeto, la depuración de la prilocaina excedía de manera apreciable el flujo sanguíneo hepático normal y, por lo tanto, se postuló la existencia de un punto extra-hepático del metabolismo de la prilocaina.

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EFFECT OF I.V. ADMINISTRATION OF LIGNOCAINE AND TETRODOTOXIN ON SENSORY UNITS IN THE TOOTH OF THE CAT

G. HAEGERSTAM

SUMMARY

A study in cats was designed to investigate the blocking of sensory nerve terminals by i.v. injection of lipid-soluble local anaesthetics such as lignocaine. I.v. injection of lignocaine 15–30 mg kg^{-1} did not completely block sensory nerve endings in the tooth of the cat, whilst tetrodotoxin (TTX) in large non-toxic doses did so. Based on the i.v. doses of TTX and the relationship between the local anaesthetic potency of the two substances when injected intra-arterially, it was calculated that lethal doses of i.v. administered lignocaine are necessary to block sensory nerve endings. It seems unlikely that peripheral pain pathways can be blocked by systemic i.v. injections of local anaesthetics.

Local anaesthetics given by systemic i.v. injection have been used for the treatment of chronic and post-operative pain (Bonica, 1954; de Jong, 1970). Recently, a case of adiposis dolorosa (Dercum's disease) was treated by i.v. administration of lignocaine 400 mg (Iwane et al., 1976). Although, it has been shown that safe doses of local anaesthetics exert little effect on peripheral nerves such as the saphenous nerves in the cat (de Jong and Nace, 1968), the possibility has been suggested that the terminals of the sensory nerves may be blocked (de Jong, 1970).

By using a method originally developed by Scott and Tempel (1963) it is possible to study nerve impulse activity originating in intradental sensory nerve terminals (Haegerstam, 1976a). Using this technique, we have studied the effect of i.v. injection of local anaesthetics on sensory nerve terminals.

The aim of the present study was to investigate the possibility of effecting blockade of terminal sensory units by systemic i.v. administration of a lipid-soluble local anaesthetic (lignocaine) and, for comparison, a lipid-insoluble toxin with local anaesthetic properties (tetrodotoxin).

MATERIAL AND METHODS

Nerve impulse activity induced in different ways in the tooth of the cat can be recorded using electrodes introduced into dental cavities (Scott & Tempel, 1963; Edwall and Scott, 1971; Arwill et al., 1973). It has recently been shown that the recorded impulses originate from sensory nerve terminals in the pulp (Arwill et al., 1973; Haegerstam, 1976a). The present experiments were conducted on 13 adult cats (2–4 kg in weight and 1–3 yr old) anaesthetized with chloralose 40 mg kg^{-1} and urethane 50 mg kg^{-1}. The experimental procedure was similar to that described by Haegerstam, Olgart and Edwall (1975). Two cavities were prepared in the dentine, one over the pulp horn and the other within the gingival part of the crown, leaving 0.1–0.3 mm of intact dentine over the pulp. The cavities were filled with isotonic saline solution and Plastibase (Squibb) insulating gel was applied around the cavities. Platinum–iridium recording electrodes were placed in contact with the exposed dentine in order to record impulse activity from intradental sensory nerves. A conventional technique was used to display the signals on a cathode-ray oscilloscope and to record the signals on magnetic tape (Edwall and Scott, 1971). Steady-state impulse activity of long duration was induced by means of local application of aconitine to the coronal cavity (Haegerstam, 1976b).

A cannula was inserted into the trachea and the temperature of the respired air was recorded in order to monitor ventilation. Femoral arterial pressure was recorded using an appropriate transducer. The impulse frequency of the pulp nerves, the temperature of the respired air and the arterial pressure were recorded on the same paper. The cranial part of the cut sympathetic and the caudal part of the cut vagus nerves were stimulated electrically and the responses to stimulation of the former estimated by observing the eye. The effect of vagus nerve stimulation was assessed by observation of arterial pressure and

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bradycardia. Lignocaine was administered i.v. both as a single injection and as repeated small increments at 5-min intervals. Tetrodotoxin (TTX) was administered i.v. as a single injection. A branch of the external carotid artery (posterior auricular artery) was used for intra-arterial injection of both compounds.

Solutions of lignocaine HCl (Astra Läkemedel AB, Södertälje, Sweden) (mol. wt 271) and tetrodotoxin (Sankyo Company Ltd, Tokyo, Japan) (mol. wt 319) were prepared in isotonic saline.

RESULTS

I.v. injection of lignocaine

Rapid i.v. injection of lignocaine hydrochloride 20 mg kg^{-1} caused respiratory and cardiac arrest. However, three injections of lignocaine 5 mg kg^{-1} at 5-min intervals caused a transient decrease in pulp nerve impulse activity. With four injections of lignocaine 5 mg kg^{-1} there was a transient but pronounced decrease in pulp activity. I.v. administration of lignocaine in accumulated doses of 10 (2 × 5), 20 (4 × 5) and 25 (5 × 5), mg kg^{-1} did not completely block aconitine-induced nerve impulse activity in the tooth. The response to vagus nerve stimulation (bradycardia and decreased systemic arterial pressure) disappeared at a cumulative i.v. dose of 15–20 (3 × 5–4 × 5) mg kg^{-1}. The response of the eye to electrical stimulation of the sympathetic nerve was blocked by doses of 20–25 (4 × 5–5 × 5) mg kg^{-1} (table I). A pronounced decrease in systemic arterial pressure of duration 1–2 min was seen after the injection of a total of 10–20 (2 × 5–4 × 5) mg kg^{-1}. The larger dose induced a transient (duration 60 s) respiratory arrest. The injection of 25 (5 × 5) mg kg^{-1} produced cardiac arrest followed by permanent respiratory arrest (table I).

Intra-arterial injection of lignocaine

Lignocaine 0.5 mg (4 mmol litre^{-1}) injected i.a. to the tooth did not affect aconitine-induced nerve impulse activity. On the other hand, 1 mg (7.5 mmol litre^{-1}) and 2 mg (15 mmol litre^{-1}) caused a transient decrease and block in nerve impulse activity, respectively (table I). Lignocaine i.a. did not affect respiration or arterial pressure in the doses used.

I.v. injection of tetrodotoxin (TTX)

The i.v. injection of TTX 2 µg kg^{-1} produced an immediate block of aconitine-induced nerve impulse activity in the tooth (fig. 1 and table I). The duration of a typical block by TTX was about 2 h. There was no response to local application of 9% NaCl, 10% KCl or acetylcholine (ACh) 1 mg ml^{-1} after TTX blockade, and this indicates that the sensory elements of the tooth were blocked to different chemical stimuli.

There was a pronounced decrease in systemic arterial pressure produced by this injection, but no effect on respiration. The duration of the decrease in arterial pressure was about 1 min after i.v. injection of TTX 2 µg kg^{-1}. The response to vagus nerve stimulation disappeared after a dose of 4 µg kg^{-1}

TABLE I. *Effects of lignocaine and tetrodotoxin (TTX) administered i.v. or i.a. in different doses*

Drug	Route of admin.	Dose	Pulp nerve activity	Vagus nerve stimulation bradycardia	Sympathetic nerve stimulation—eye response	Respiration	Systemic arterial pressure
Lignocaine	i.v.	10 mg kg^{-1}	unchanged	unchanged	unchanged	decreased	decreased
		15 mg kg^{-1}	decreased	decreased	unchanged	decreased	decreased
		20 mg kg^{-1}	decreased	abolished	decreased	decreased	decreased
		30 mg kg^{-1}	decreased	abolished	abolished	arrest	zero
Lignocaine	i.a.	0.5 mg	unchanged				
		1.0 mg	decreased				
		2.0 mg	abolished				
TTX	i.v.	2 µg kg^{-1}	abolished	unchanged	unchanged	unchanged	decreased
		4 µg kg^{-1}	abolished	abolished	abolished	unchanged	decreased
		8 µg kg^{-1}	abolished	abolished	abolished	arrest	zero
TTX	i.a.	0.1 µg	decreased				
		0.2 µg	abolished				

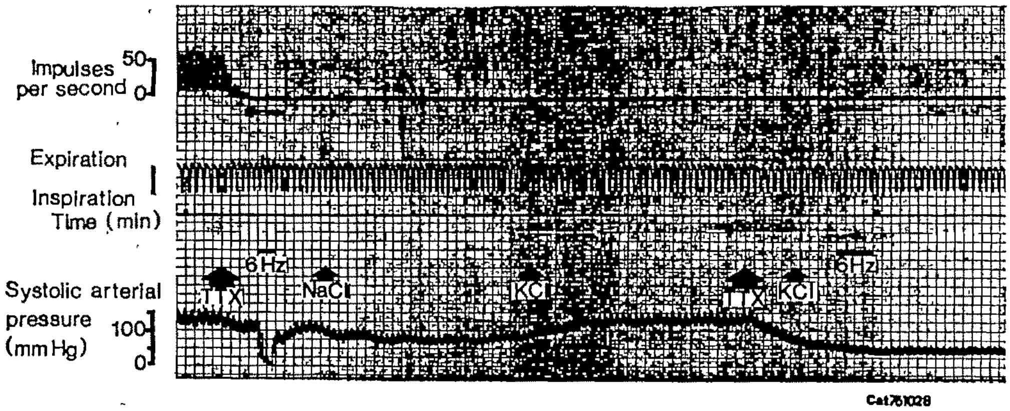

FIG. 1. The effect of i.v. tetrodotoxin 2 μg kg^{-1} (first arrow) and 4 μg kg^{-1} (total) (second arrow) on the frequency of pulp nerve impulses, respiration and systemic arterial pressure. Stimulation of the vagus nerve (6 V, 6 Hz) is indicated by a line. NaCl 9% and KCl 10% were applied locally to the coronal tooth cavity (small arrows).

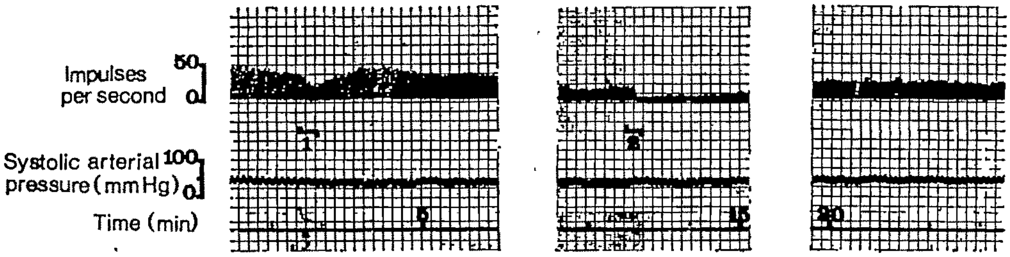

FIG. 2. The effect of i.a. tetrodotoxin 0.1 mg (1) and 0.2 mg (2) on the frequency of pulp impulse activity and systemic arterial pressure.

and the response to sympathetic nerve stimulation was blocked after a dose of 8 μg kg^{-1} of TTX (table I). At this dose there was respiratory and cardiac arrest.

Intra-arterial injection of TTX

TTX injected i.a. in a concentration of 0.1 μg (6.3×10^{-7} mol $litre^{-1}$) decreased the frequency of aconitine-induced spikes. An injection of 0.2 μg (1.3×10^{-6} mol $litre^{-1}$) TTX produced complete block of nerve impulse activity (fig. 2, table I). The duration of such a block was about 3 min. TTX injected i.a. in this concentration did not affect respiration or arterial pressure.

DISCUSSION

Toxic doses of lignocaine injected i.v. produced a transient decrease in pulp sensory nerve impulse activity, while tetrodotoxin administered by the same route in non-toxic doses caused a persistent block of the same nerve activity. Intra-arterial administration in non-toxic doses of both lignocaine and tetrodotoxin blocked pulp nerve activity.

The weak blocking effects of i.v. lignocaine cannot be explained by an impaired circulation resulting from hypotension, since tetrodotoxin (TTX) did block dental nerve impulse activity, despite producing profound hypotension.

Local anaesthetics similar to lignocaine pass readily from the vascular to the perineural space (de Jong and Nace, 1968). The lipid-insoluble compound tetrodotoxin (TTX), which is rapidly and uniformly distributed in the body water (Mosher et al., 1964) also reaches the perineural space. The i.v. administration of TTX in a dose of 2–3 μg kg^{-1} was obviously sufficient to block the nerves in the tooth. Uniform distribution of this quantity in the body water would result in a 10^{-8}-mol $litre^{-1}$ concentration of TTX, which is a reasonable blocking concentration (Mosher et al., 1964). The long duration of block of pulp nerve activity caused by i.v. TTX may be a result of slow elimination. This suggestion may be supported by the long duration of a TTX intoxication described by Captain Cook in 1772 (Beaglehole, 1961).

Severe depression of respiration was seen with doses of i.v. lignocaine that only slightly decreased pulp nerve impulse activity, while this activity was blocked completely by i.v. TTX without any signs of c.n.s. toxicity. These results may be explained on the basis that the TTX molecule is lipid-insoluble and too large to penetrate the pores in the blood–brain barrier (Wang et al., 1972).

The ratio between the blocking doses of TTX and lignocaine administered i.a. in the present study was found to be $1:1\times10^4$, which agrees with the ratio $1:6\times10^3$, calculated from the concentrations of TTX and lignocaine required to block frog sciatic nerve (Adams, Blair and Takman, 1976). Based on this ratio and the dose of TTX which blocks pulp nerve activity and assuming that lignocaine was distributed uniformly in the body water, it can be calculated that 20 mg kg^{-1} of lignocaine would be required to block pulp nerve activity. However, the volume of distribution is 91 litre (human data, Covino and Vassallo, 1976), which indicates that the lignocaine is not distributed uniformly, but accumulates to some extent in the tissues. Thus, the estimated dose of i.v. lignocaine necessary to block peripheral nerve activity would be more than 20 mg kg^{-1}, which is greater than the lethal dose. The LD_{50} in the cat is 20 mg kg^{-1} (de Jong, 1970). However, it is possible to produce nerve block in a limb by i.v. administration of a local anaesthetic when blood flow in the limb is isolated from the central circulatory compartment by means of a tourniquet. The dose necessary for producing blockade of nerves in the limb is relatively small in relation to the total circulation, especially when the limb is exsanguinated before injection of the local anaesthetic.

It is concluded that peripheral nerve blocks cannot be induced by systemic i.v. injection of non-toxic doses of lipid-soluble local anaesthetics such as lignocaine.

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EFFET DE L'ADMINISTRATION INTRAVEINEUSE DE LIGNOCAINE ET DE TETRODOTOXINE SUR LE SIEGE DU PAQUET VASCULO-NERVEUX DE LA DENT DU CHAT

RESUME

On a effectué une étude sur des chats, afin de déterminer le blocage des points terminaux du nerf sensitif par l'injection intraveineuse d'agents anesthésiants locaux solubles dans les lipides, tels que la lignocaïne. L'injection de lignocaïne par voie intraveineuse (à raison de 15–30 mg kg^{-1}) n'a pas complètement bloqué les extrémités du nerf sensitif de la dent du chat, alors que la tétrodotoxine (TTX), en grandes doses non toxiques, l'a fait. En se basant sur les doses intraveineuses de TTX et sur la relation qui existe entre l'efficacité anesthésique locale des deux substances lorsque celles-ci sont injectées par voie intra-artérielle, on a calculé qu'il faudrait des doses mortelles de lignocaïne administrées par voie intraveineuse pour bloquer les extrémités du nerf sensitif. Il semble improbable que l'on puisse bloquer les voies d'accès de la douleur périphérique par des injections intraveineuses systémiques d'agents anesthésiques locaux.

DIE WIRKUNG INTRAVENÖSER VERABREICHUNG VON LIGNOCAIN UND TETRODOTOXIN AUF DIE NERVEN IM ZAHN EINER KATZE

ZUSAMMENFASSUNG

Eine Studie bei Katzen war darauf angelegt, die Blockierung von Nervenenden durch intravenose Injektion lipidlöslicher Lokalanästhesiemittel wie etwa Lignocain. Die intravenöse Injektion von 15–30 mg/kg Lignocain blockierte die Nervenenden im Katzenzahn nicht vollig, wahrend dies bei grossen, nicht-toxischen Dosen von Tetrodotoxin (TTX) der Fall war. Ausgehend von den intravenosen Dosen von TTX, und von dem Verhältnis der lokalanästhetischen Wirksamkeit der beiden Substanzen im Falle einer intraarteriellen Injektion wurde errechnit, dass lethale Dosen von intravenös verabreichtem Lignocaine notwendig waren, um die Nervenenden vollig zu blockieren. Es scheint unwahrscheinlich, dass die peripheren Schmerzwege durch systemische intravenose Injektionen lokaler Betäubungsmittel blockiert werden können.

EFECTO DE LA ADMINISTRACION INTRAVENOSA DE LIGNOCAINA Y DE TETRODOTOXINA EN LAS UNIDADES SENSORIALES DEL DIENTE DE GATO

SUMARIO

El estudio en los gatos tenía por objeto averiguar el bloqueo de los terminales nerviosos sensoriales mediante la inyección i.v. de anestésicos lipido-solubles locales, tales como lignocaina. La inyección i.v. de 15–30 mg kg^{-1} de lignocaina no bloqueó totalmente las terminaciones nerviosas sensoriales en el diente del gato, mientras que se producía el bloqueo con la tetrodotoxina (TTX) en grandes dosis no-tóxicas. Basándose en las dosis i.v. de TTX y en la relación entre la potencia anestésica local de las dos substancias inyectadas intra-arterialmente, se calculó que se necesitan dosis letales de lignocaina inyectada i.v. para bloquear las terminaciones nerviosas sensoriales. Parece poco probable que las vías del dolor periférico pueden bloquearse mediante inyecciones i.v. sistémicas de anestésicos locales.

Br. J. Anaesth. (1979), **51**, 493

PLASMA CONCENTRATIONS OF MEDAZEPAM AND ITS METABOLITES AFTER ORAL ADMINISTRATION

D. M. HAILEY AND E. S. BAIRD

SUMMARY

The plasma concentrations of medazepam and its metabolites, diazepam and desmethyldiazepam, were determined in volunteer subjects following the oral administration of medazepam 10 mg. The results indicated that medazepam was absorbed rapidly, that low concentrations of metabolites were present during the 1st h, and that the build-up in the circulation of the major metabolite, desmethyldiazepam, was prolonged and variable. As many of the clinical effects and possible adverse reactions of medazepam appear to be associated with the presence of this major metabolite, the metabolic and pharmacokinetic characteristics of the drug should be considered when using medazepam as an anxiolytic before dentistry or surgery.

Medazepam (7-chloro-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepine; Nobrium) is used widely in the management of anxiety states. The chemically related drug diazepam, when administered orally, has been shown to be effective in allaying apprehension in patients undergoing conservative dentistry (Baird and Curson, 1970) and medazepam also has been found to give good results in this field (authors' unpublished results).

In view of the useful data obtained from an analysis of the plasma concentrations of diazepam and its metabolites following oral administration (Baird and Hailey, 1972), we have conducted similar studies with medazepam. Relatively little information is available concerning the plasma concentrations of medazepam and its metabolites in clinical practice. De Silva and Puglisi (1970) included data on the plasma concentrations which had been obtained during the development of their gas chromatographic method for the determination of medazepam, diazepam and their metabolites. Mallach, Moosmayer and Rupp (1973) presented data on the plasma concentrations of medazepam and its metabolites in support of a chromatographic method while Bond, Hailey and Lader (1977) included measurement of the ratios of medazepam to two of its major metabolites in an assessment of the effects of benzodiazepines on anxiety states in patients receiving continuous treatment with these drugs. The data presented here provide further information on the absorption and distribution of medazepam and its metabolites after oral administration and may be of help in the assessment of the efficacy and use of this drug.

METHODS

Two groups of healthy male volunteers, aged 21–24 yr, were studied. Subjects in each group received an oral dose of medazepam 10 mg (one capsule) with 200 ml of water. A light breakfast was permitted about 2 h before the administration of the drug. Food was withheld from the subjects in group 1 until 4 h after administration and from those in group 2 for the duration of the sampling period. Blood samples were taken by venepuncture over 48 and 72 h from the four subjects in group 1 and over 60 min from the three subjects in group 2, using the sampling times shown in figure 1 and table I. It was necessary to split the sampling times in this fashion because of the large number of venepunctures required. After collection, blood samples were oxalated, centrifuged and the plasma separated and stored at −18 °C until analysis. The plasma concentrations of medazepam and its metabolites, diazepam and desmethyldiazepam, were measured by electron-capture gas chromatography (Baird, Hailey and Malcolm, 1973) using a Pye-Unicam model 104 chromatograph.

RESULTS

The plasma concentrations in group 1 are shown in figure 1. Maximum concentrations of medazepam were obtained in three subjects at 1.5 h after ingestion and

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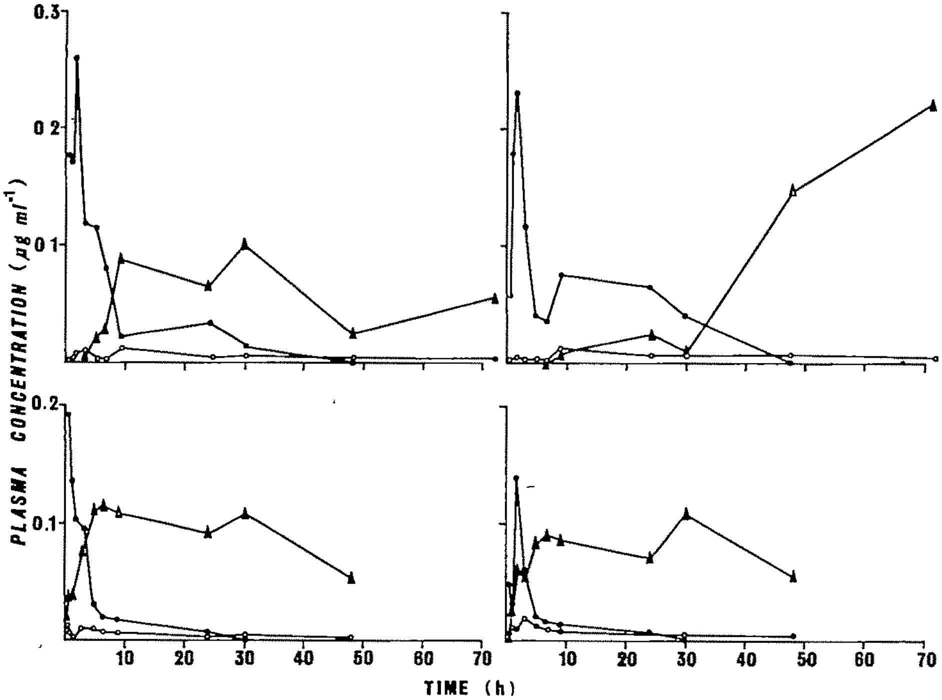

FIG. 1. Plasma concentration–time curves for medazepam, diazepam and desmethyldiazepam for four subjects (group 1) following oral administration of medazepam 10 mg. ●——● = medazepam, ○——○ = diazepam, ▲——▲ = desmethyldiazepam.

TABLE I. *Plasma concentrations of medazepam* ($\mu g\ ml^{-1}$) *in three subjects* (*group* 2)

Time after administration (min)	Subject 1	Subject 2	Subject 3
10	<0.01	<0.01	0.10
20	0.10	0.15	0.27
30	0.31	0.18	0.27
40	0.22	0.20	0.28
50	0.17	0.51	0.31
60	0.19	0.31	0.13

at 0.5 h in the fourth. The mean peak concentration was 0.21 $\mu g\ ml^{-1}$ with a range of 0.14–0.26 $\mu g\ ml^{-1}$. The concentrations decreased rapidly from the maximum value, and in all subjects were less than 0.01 $\mu g\ ml^{-1}$ at 48 h. Diazepam was present in all subjects at 0.5 h and persisted at a low concentration for at least 48 h. There was a considerable variation in the build up of desmethyldiazepam. In two subjects this metabolite was detected after 0.5 h, while in the other two it appeared initially at 3 h and 9 h respectively. From the later results, it can be seen (fig. 1) that the concentration of desmethyldiazepam increased beyond the 24-h period. In the subject in whom the initial appearance of desmethyldiazepam was at 9 h, the plasma concentrations increased over a 72-h period.

The concentrations of medazepam found in the second group of subjects are presented in table I and show that medazepam was absorbed rapidly, the compound being present in the circulation of one subject at 10 min and in all three at 20 min. There was some fluctuation in the concentrations, possibly associated with incomplete distribution of the drug on this short time-scale. In all three subjects, diazepam was detected at 10 min at a concentration of 0.003 $\mu g\ ml^{-1}$ and persisted at about this value over the 60-min period. Desmethyldiazepam appeared at 10 min in one subject, at 20 min in the second, and was not detected over the 60-min period in the third. In the two subjects in whom it was detected, the plasma concentration fluctuated between 0.005 and 0.002 $\mu g\ ml^{-1}$.

The method used (electron-capture gas chromatography) has poor sensitivity for desmethylmedazepam; this metabolite was not detected in any sample in either group.

DISCUSSION

The plasma concentrations of medazepam and its metabolites and the rates of absorption of medazepam found in this study are in agreement with those reported by de Silva and Puglisi (1970) and Mallach, Moosmayer and Rupp (1973). The former reported a peak concentration of medazepam 0.98 $\mu g\ ml^{-1}$ 1 h after a 50-mg dose, with concentrations at 24 h of 0.07 $\mu g\ ml^{-1}$, 0.02 $\mu g\ ml^{-1}$ and 0.19 $\mu g\ ml^{-1}$ respectively for medazepam, diazepam and desmethyldiazepam. Mallach and co-workers (1973) found a peak concentration of 0.66 $\mu g\ ml^{-1}$ medazepam after a 40-mg dose with concentrations at 24 h of about 0.02 $\mu g\ ml^{-1}$ for medazepam and diazepam and 0.19 $\mu g\ ml^{-1}$ for desmethyldiazepam. These workers noted also that the plasma concentrations of medazepam fluctuated after the peak concentration had been reached. Similar effects were noted in three of the four subjects in group 1 of the present study.

The results show that absorption of medazepam is rapid after oral administration and that low concentrations of its metabolites are present in the circulation during the 1st hour. Desmethylmedazepam, which was not detected in this study, was shown by Mallach, Moosmayer and Rupp (1973) to reach a maximum plasma concentration of 0.17 $\mu g\ ml^{-1}$ 1 h after the administration of medazepam 40 mg. Diazepam appears in the circulation before desmethyldiazepam, but then persists at low concentrations during the elimination phase. The latter compound, formed primarily by oxidation of desmethylmedazepam, is the major metabolite of medazepam. Plasma concentrations of desmethyldiazepam increase for at least 24 h after administration, and many of the clinical effects of medazepam must be attributed to this metabolite. The pharmacological effects of medazepam and desmethylmedazepam are unclear. Assaf, Dundee and Bali (1975) found that when used as oral preanaesthetic medication, medazepam 10 mg produced less drowsiness than a similar dose of diazepam and was no more anxiolytic than placebo. Their data were obtained over a 90-min period after the administration of the drug, which would correspond to the time of maximum plasma concentrations of medazepam and desmethylmedazepam while the concentrations of diazepam and desmethyldiazepam would be very low. Bond, Hailey and Lader (1977) found that in anxious patients receiving a continuous dosage of medazepam, there appeared to be a correlation between the plasma concentrations of medazepam and physiological effects, but no correlation was found between plasma concentrations and clinical ratings or behavioural measurements. Therefore, the rapid absorption of medazepam would seem to be of questionable significance as regards clinical benefit, and its efficacy as an anxiolytic would seem to be largely attributable to the presence of its metabolite desmethyldiazepam. As the appearance of this metabolite in the circulation is delayed, it would seem appropriate for medazepam to be administered at least 8 h before an anxiolytic effect is desired. Medazepam appears to be an effective anxiolytic when administered to patients the night before undergoing conservative dentistry (authors' unpublished results) and this seems consistent with its metabolic profile.

From the previous discussion, it follows that medazepam must be grouped with those benzodiazepines which have most of their activity related to the formation of desmethyldiazepam and are effectively pro-drugs for this compound. Benzodiazepines of this type include fosazepam (Nicholson, Stone and Clarke, 1976), potassium chlorazepate (Nicholson et al., 1976) and clazepam (Giudicelli et al., 1978).

In the study reported here, the appearance of desmethyldiazepam in the circulation of one of the subjects in group 1 was delayed markedly and plasma concentrations were still increasing at 72 h. This would seem to indicate that the pharmacological response might be delayed significantly in some patients. Desmethyldiazepam will, in any case, remain in the circulation in significant quantities for at least 2 days after the administration of a single therapeutic dose of medazepam, and appropriate precautions should be taken where necessary. Prolonged administration of diazepam has been shown to lead to accumulation of the desmethyl metabolite (Gamble, Dundee and Gray, 1976) and a similar result can be expected after prolonged administration of medazepam. De Silva and Puglisi (1970) noted that the metabolite accumulated, a plasma concentration of 0.45 $\mu g\ ml^{-1}$ being obtained at 96 h after four 50-mg doses given at 24-h intervals. In the group of patients studied by Bond, Hailey and Lader (1977) the mean plasma concentration of desmethyldiazepam was 0.71 $\mu g\ ml^{-1}$, using a mean dosage of medazepam 27 mg per day. The mean plasma concentration of desmethyldiazepam in these patients after diazepam 11 mg per day was 0.32 $\mu g\ ml^{-1}$, so that the concentrations of desmethyldiazepam after each treatment are similar.

The data obtained in this study clarify further the possible uses and disadvantages of medazepam. The clinical effects and potential adverse reactions of this drug would appear to depend primarily on its main active metabolite and to be linked to the rate of appearance of this compound in the circulation. This should be borne in mind when using medazepam as premedication before dentistry or surgery.

Note added in proof. Möhler and Okada (1978) have determined the degree of binding of benzodiazepines to selective benzodiazepine receptors in human brain by measuring the displacement of tritium-labelled diazepam. They have drawn attention to the correlation between the degree of binding to the receptor and pharmacological activity for a series of compounds. It is of interest that medazepam binds to the specific receptor more than 100 times less strongly than diazepam, the apparent dissociation constants for the compounds being 880 and 7.4 nmol respectively. These results support the suggestion that medazepam has rather weak pharmacological activity and that its therapeutic efficacy depends on its active metabolites.

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CONCENTRATION DE MEDAZEPAM ET DE SES METABOLITES DANS LE PLASMA APRES ADMINISTRATION ORALE

RESUME

Les concentrations de médazépam et de ses métabolites, diazépam et desméthyldiazépam, dans le plasma ont été déterminées sur des volontaires après administration orale de 10 mg de médazépam. Les résultats ont fait ressortir que le médazépam avait été rapidement absorbé, qu'il y avait de faibles concentrations de métabolites au cours de la premiére heure et que la concentration dans la circulation du principal métabolite, le desméthyldiazépam, a été prolongée et variable. Comme de nombreux effects cliniques et de nombreuses réactions adverses du médazépam semblent être associés à la présence de ce métabolite principal, il faut tenir compte des caractéristiques métaboliques et pharmacocinétiques de ce médicament lorsqu'on utilise le médazépam en tant qu'agent anxiolytique avant toute intervention chirurgicale ou toute application dentaire.

PLASMAKONZENTRATIONEN VON MEDAZEDAM UND SEINEN METABOLITEN NACH MÜNDLICHER VERABREICHUNG

ZUSAMMENFASSUNG

In freiwilligen Versuchspersonen wurden nach mündlicher Verabreichung von 10 mg Medazepam die Plasmakonzentrationen von Medazepam und seinen Metaboliten Diazepam und Desmethyldiazepam bestimmt. Die Ergebnisse deuteten darauf hin, dass Medazepam schnell absorbiert wurde, dass während der ersten Stunde geringe Konzentrationen an Metaboliten vorhanden waren, und dass sich das Hauptmetabolit Desmethyldiazepam im Kreislauf uber längere Zeit und unterschiedlich aufbaute. Da viele der klinischen Wirkungen und moglichen nachteiligen Rückwirkungen von Medazepam mit dem Vorhandensein dieses Hauptmetaboliten im Zusammenhang zu stehen scheinen, sollten bei Verwendung von Medazepam als angstlosendes Mittel vor Zahnorthopädie bzw. Chirurgie die metabolischen und pharmakokinetischen Charakteristika des Arzneimittels in Betracht gezogen werden.

CONCENTRACIONES DE PLASMA DEL MEDAZEPAM Y SUS METABOLITOS DESPUES DE ADMINISTRACION ORAL

SUMARIO

Las concentraciones de plasma del medazepam y sus metabolitos, diazepam y desmetildiazepam, fueron determinadas en sujetos voluntarios, después de administrarseles 10 mg de medazepam. Los resultados indicaron que el medazepam se absorbía rápidamente, que existían bajas concentraciones de metabilitos durante la primera hora y que la formación en la circulación del metabolito principal, desmetildiazepam, era variable y prolongada. Como muchos de los efectos clínicos y de las posibles reacciones contrarias del medazepam parecen ser asociados con la presencia de este metabolito principal, hay que examinar las características metabólicas y farmacocinéticas del producto cuando se usa el medazepam como ansiolítico antes de las intervenciones dentales o quirúrgicas.

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A COMPARISON OF THE RESPIRATORY EFFECTS OF MEPTAZINOL, PENTAZOCINE AND MORPHINE

C. JORDAN, J. R. LEHANE, P. J. ROBSON AND J. G. JONES

SUMMARY

The respiratory effects of a new strong analgesic, meptazinol, were compared with a placebo and with equianalgesic doses of morphine and pentazocine in a double-blind crossover trial in seven healthy volunteers. No significant change in the ventilatory response to rebreathing carbon dioxide was observed after meptazinol 100 mg/70 kg or placebo. However, both morphine 10 mg/70 kg and pentazocine 60 mg/70 kg depressed the slope of the ventilatory response (−30.0% and −31.6% respectively, $P < 0.02$, averaged over the first 3.5-h period). End-tidal carbon dioxide tension (PE'_{CO_2}) while breathing room air increased significantly following all three drugs. However, the increase in PE'_{CO_2} after meptazinol (0.22 kPa averaged over 3.5 h) was significantly less than that following morphine (0.40 kPa, $P < 0.05$) and pentazocine (0.59 kPa, $P < 0.01$). While breathing room air with a resistive inspiratory load of 8 kPa litre^{-1} s, PE'_{CO_2} again increased significantly ($P < 0.05$) following all three drugs. The increase in PE'_{CO_2} after meptazinol was then the same as that after morphine (0.51 kPa averaged over 3.5 h). The increase following pentazocine (0.80 kPa) was significantly greater than that after both morphine and meptazinol ($P < 0.02$).

Doses of analgesics adequate for complete pain relief are often withheld because of the danger of inducing respiratory depression and physical or psychological dependence. A potent analgesic with negligible depressant effects on respiration would be particularly useful when pain relief is required in patients with poor pulmonary function, in women at term and during the period after operation. If such a drug were also free of abuse potential it would offer considerable advantages over the established opiate drugs.

Meptazinol (m (3-ethyl-1-methyl hexahydro 1-H-azepin-3-yl)phenol hydrochloride, Wyeth Laboratories) is an opioid antagonist drug with analgesic properties. It has been shown to produce significant pain relief in doses of 60–150 mg/70 kg i.m. in patients recovering from abdominal surgery (Paymaster, 1976, 1977). There was no evidence of physical dependence in experiments in rats (Goode and White, 1971) and in the monkey (Swain, Villancal and Seevers, 1973). Observations in animals (K. Rhodes, personal communication) and man (Verschraegen et al., 1976) have shown that meptazinol is relatively free of respiratory side-effects, although this has not been investigated formally in man. We have studied the respiratory effects of meptazinol in human subjects and compared these effects with those of morphine, pentazocine and placebo.

METHODS

Seven healthy male volunteers aged 25–33 yr gave informed consent for this study, which was carried out with the approval of the Hospital Ethics Committee. Each subject was studied on four non-consecutive days on each of which he was given meptazinol 100 mg/70 kg, morphine 10 mg/70 kg, pentazocine 60 mg/70 kg or 2 ml of 0.9% saline by i.m. injection. The injections were administered in a double-blind manner and in a random order which was different for each subject.

Three tests of the respiratory effects of these drugs were used:

(1) The ventilatory response to hypercapnia ($\dot{V}E/PE'_{CO_2}$) was determined by a modified Read rebreathing method similar to that developed by Milledge, Minty and Duncalf (1974). Ventilation was measured using an Ohio spirometer and carbon dioxide concentration was measured using a Godart infra-red analyser. The rebreathing test was performed in duplicate on each occasion.

(2) The end-tidal $P\text{CO}_2$ (PE'_{CO_2}) was measured with the subjects breathing room air via a non-rebreathing valve (Hook and Tucker, London) over a period of 7 min. The mean PE'_{CO_2} during each 1-min interval was derived electronically.

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(3) The effect of an inspiratory load of 8 kPa litre^{-1} s on the regulation of ventilation was determined from measurements of $P\mathrm{E}'_{CO_2}$ over 7 min. The resistive load was connected to the inspiratory limb of the non-rebreathing valve.

Following a light breakfast, subjects arrived at the laboratory at 9.00 a.m. and rested for 30 min. A series of control measurements followed. At 10.00 a.m. the injection was given and the tests were repeated after 15 min, 1 h, 2 h, 3 h and 4 h. The subjects then ate a light lunch and a final series of measurements was made at 4.00 p.m. (6 h).

During the tests great care was taken to ensure that the subjects were comfortable and undisturbed. They remained supine throughout and listened to music via headphones.

The data from each of the tests were analysed in the following manner.

The ventilatory response to hypercapnia

The slopes of $\dot{V}\mathrm{E}/P\mathrm{E}'_{CO_2}$ response curves were determined by drawing a line of best fit through the linear portion of each curve. The intercepts were determined by extrapolating these lines of best fit to zero ventilation. The control data were the means of duplicate measurements made at the start of the day since the within-day variability of $\dot{V}\mathrm{E}/P\mathrm{E}'_{CO_2}$ curves is much less than between-day variability (Jennett, 1968; Sahn et al., 1977).

Slopes obtained following injection were compared with control data from the same day by calculating:

$$\Delta \text{ slope} = \log_{10} (\text{test slope}) - \log_{10} (\text{mean control slope})$$

Logarithms of the slopes were used to permit the application of standard *t* tests to the data because the distribution of $\dot{V}\mathrm{E}/P\mathrm{E}'_{CO_2}$ slopes in the population is skewed (log normal) (Irsigler, 1976; Mustchin, 1977).

The above equation can be re-written:

$$\Delta \text{ slope} = \log_{10} (\text{test slope/mean control slope})$$

By taking antilog_{10} (Δ slope), changes in slope may be expressed as ratios. Mean changes in slope calculated by this method are geometric means.

Intercepts were compared with control data from the same day by calculating (test intercept − mean control intercept).

$P\mathrm{E}'_{CO_2}$ while breathing at rest

Our previous observations had shown that the between-day variability of $P\mathrm{E}'_{CO_2}$ is similar to that within a day and also that there was a small increase during the course of the day. The control used, therefore, was mean $P\mathrm{E}'_{CO_2}$ obtained over the first 4 h after injection of saline. Test data were compared with this mean by calculating (test $P\mathrm{E}'_{CO_2}$ − mean control $P\mathrm{E}'_{CO_2}$).

$P\mathrm{E}'_{CO_2}$ while breathing with the inspiratory load

Test $P\mathrm{E}_{CO_2}$ was compared with control $P\mathrm{E}'_{CO_2}$ whilst breathing with the load in a similar way:

test $P\mathrm{E}'_{CO_2}$ (loaded) − mean control $P\mathrm{E}'_{CO_2}$ (loaded)

Statistical analysis

In order to compare data obtained after each injection with control values the means of $\dot{V}\mathrm{E}/P\mathrm{E}'_{CO_2}$ slopes and intercepts, and $P\mathrm{E}'_{CO_2}$ measurements were calculated at each time interval. Differences between these values and control values were obtained as described above and tested using the unpaired (two-sample) *t* test.

In order to perform a useful comparison between the drugs, the average of the results of the first four measurements after injection (over the first 3.5-h period) was obtained. Differences in $\dot{V}\mathrm{E}/P\mathrm{E}'_{CO_2}$ slopes were expressed as geometric mean percentage changes, and tested by applying the paired *t* test to the log data. Changes in $P\mathrm{E}'_{CO_2}$ were expressed as mean differences with the variability expressed as the standard error of the difference (SED) and tested by means of paired *t* tests.

RESULTS

The ventilatory response to hypercapnia

Morphine and pentazocine produced significant depression of the $\dot{V}\mathrm{E}/P\mathrm{E}'_{CO_2}$ slope whereas meptazinol and saline did not (fig. 1).

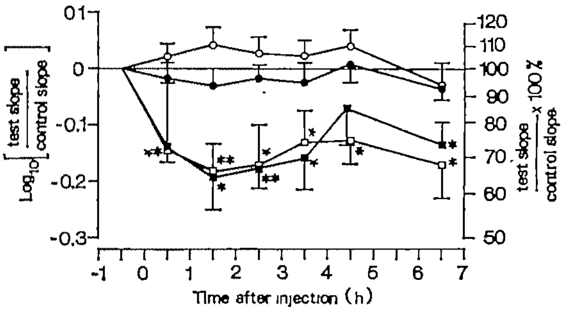

FIG. 1. Mean changes in $\dot{V}\mathrm{E}/P\mathrm{E}'_{CO_2}$ slopes (±1 SEM). $*P < 0.05$; $**P < 0.01$ (unpaired *t* test). ○ = saline; ● = meptazinol; □ = morphine; ■ = pentazocine.

TABLE I. *Slope and PE'_{CO_2} changes during the first 3.5 h after drug. Mean (SED).* $^*P<0.05$; $^{**}P<0.005$

	Meptazinol	Morphine	Pentazocine
Δ slope	−0.03 (0.02)	−0.16** (0.04)	−0.17* (0.05)
(% slope change)	−6.7	−30.0**	−31.8*
Change in resting PE'_{CO_2} (kPa)	0.22* (0.08)	0.41** (0.05)	0.59** (0.08)
Change in loaded PE'_{CO_2} (kPa)	0.51* (0.13)	0.51** (0.10)	0.80** (0.11)

Changes in slope from control values for the 3.5-h period following injection are shown in table I. The change following both morphine and pentazocine was greater than that after meptazinol, the difference being 25.4% ($P<0.02$) and 26.8% ($P<0.05$) respectively. It should be noted that these values are not the arithmetic differences of the results shown in table I as they are derived from the logarithmic data.

Mean changes in the intercept of the $\dot{V}E/PE'_{CO_2}$ curve were less than 0.23 kPa (SEM 0.14 kPa) and there were no significant differences between drugs and placebo.

PE'_{CO_2} while breathing at rest

The PE'_{CO_2} was increased significantly for the whole 6-h period following morphine and pentazocine and for 3 of the 6 h following meptazinol (fig. 2).

Mean changes in PE'_{CO_2} over the first 3.5 h after injection were analysed (table I). Meptazinol produced a small but significant increase compared with saline, the mean difference being 0.25 kPa (SED 0.08 kPa) ($P<0.05$), saline values being 0.03 kPa less than control. Morphine produced a greater increase in PE'_{CO_2} and the difference between morphine and meptazinol, 0.19 kPa (SED 0.05 kPa) was significant ($P<0.02$). Pentazocine produced the greatest increase in PE'_{CO_2}, being greater than morphine by 0.19 kPa (SED 0.07 kPa) ($P<0.05$). The mean PE'_{CO_2} values observed during this 3.5-h period are shown in figure 3.

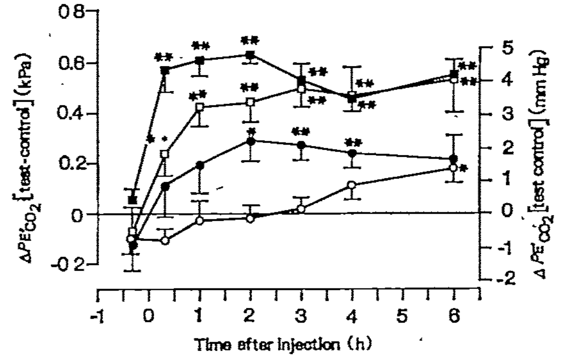

FIG. 2. Mean changes in resting PE'_{CO_2} (± SEM). $^*P<0.05$; $^{**}P<0.01$ (unpaired *t* test). ○ = saline; ● = meptazinol; □ = morphine; ■ = pentazocine.

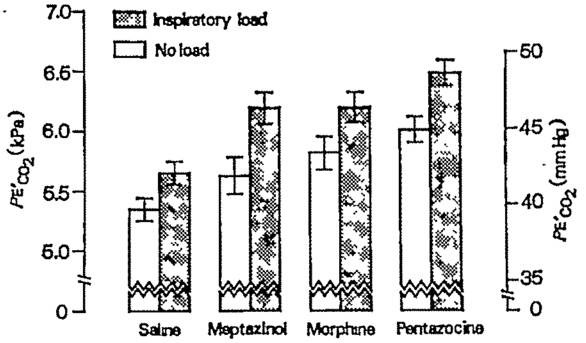

FIG. 3. Mean PE'_{CO_2} (±1 SEM) during the first 3.5 h after the drug.

PE'_{CO_2} while breathing with the inspiratory load

Following all three active drugs there was again a significant increase in PE'_{CO_2} compared with that after placebo while breathing with the load ($P<0.05$).

The average PE'_{CO_2} values during these tests over 3.5 h are shown in figure 3. Under these conditions the increase in PE'_{CO_2} after meptazinol was such that there was no longer any significant difference between it and morphine, the mean difference being 0.003 kPa (SED 0.09 kPa). The mean difference between pentazocine and meptazinol was 0.29 kPa (SED 0.05 kPa) ($P<0.02$) and between pentazocine and morphine was 0.30 kPa (SED 0.09 kPa) ($P<0.02$).

Side-effects

All three active drugs produced noticeable side-effects during the course of the study, while no side-effects were observed following the placebo (table II).

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TABLE II. *Side-effects reported among seven volunteers*

Side-effect	Morphine	Pentazocine	Meptazinol
Mild euphoria	2	—	—
Dysphoria	—	4	—
Nausea alone	2	2	1
Nausea and vomiting	1	—	4

DISCUSSION

The results of this study demonstrated that meptazinol 100 mg/70 kg body weight had a negligible effect on the slope and intercept of the ventilatory response to hypercapnia whereas morphine 10 mg/70 kg and pentazocine 60 mg/70 kg both produced large changes in slope. The changes observed following morphine and pentazocine were similar to those reported by other workers when their data were analysed by the same methods (table III).

TABLE III. *Reported results of the effects of morphine and pentazocine on ventilation*

Drug (source)	Change in $P\mathrm{E}'_{\mathrm{CO}_2}$ (kPa)	Change in slope of $\dot{V}\mathrm{E}/P\mathrm{E}'_{\mathrm{CO}_2}$ curve (%)
Morphine 7.5 mg (Weil et al., 1975)	+0.33	−42
Morphine 10 mg (Jennett, Barker and Forrest, 1968)	+0.41	−31
Morphine 10 mg (Present study)	+0.44	−34
Pentazocine 20 mg (Jennett, Barker and Forrest, 1968)	+0.59	−25
Pentazocine 45 mg (Engineer and Jennett, 1972)	+0.54	−33
Pentazocine 60 mg (Present study)	+0.64	−36

The measurement of changes in $P\mathrm{E}'_{\mathrm{CO}_2}$ during quiet breathing of room air is another direct test of respiratory depression which has proved to be repeatable and sensitive (Jennett, 1968). The consistency of the measurements in this study was such that the small increase in $P\mathrm{E}'_{\mathrm{CO}_2}$ after meptazinol could be shown to be significant. Moreover, using paired *t* tests, the effects of the three drugs were shown to differ significantly so that the increase in $P\mathrm{E}'_{\mathrm{CO}_2}$ after drug increased in the order meptazinol → morphine → pentazocine. The observed increases in $P\mathrm{E}'_{\mathrm{CO}_2}$ following morphine and pentazocine were similar to those reported by other workers (table III).

These two tests are used in the laboratory to determine the effects of drugs on the control of ventilation in man. It is possible, however, that a drug which does not produce gross changes in these tests may impair the ability of a patient with an abnormal respiratory load to maintain adequate ventilation. To investigate this possibility we studied the effects of a severe inspiratory load of 8 kPa litre^{-1} s which was the minimum necessary to produce appreciable changes in $P\mathrm{E}'_{\mathrm{CO}_2}$ in healthy volunteers. Under these conditions, after meptazinol, $P\mathrm{E}'_{\mathrm{CO}_2}$ did not differ significantly from that after morphine but both were significantly greater than after placebo. This result suggests a difference between the effects of meptazinol on non-loaded and loaded breathing. However, the clinical relevance of the effects of drugs on loaded breathing in healthy volunteers remains to be established.

In studies of the respiratory effects of drugs it is essential to compare equipotent doses of each drug. Paymaster has shown that, for pain relief after operation, meptazinol 100 mg was equianalgesic with pentazocine 60 mg and pethidine 100 mg (Paymaster, 1977). It is concluded that, for equivalent pain relief, meptazinol causes substantially less respiratory depression than morphine 10 mg and pentazocine 60 mg. Further, in a pilot study on two subjects both of whom received meptazinol 60 mg/70 kg and 150 mg/70 kg, no dose-related respiratory effects were observed. These doses cover the range used so far in pain relief after operation (Paymaster, 1976, 1977) and in obstetric analgesia (M. B. A. Jackson, personal communication).

The only side-effects of meptazinol observed in this trial were nausea and vomiting, the frequencies of which were greater than following the other drugs. However, it is known that side-effects of analgesics differ both in type and severity in patients in pain and in normal pain-free subjects (Dundee, 1977). In patients recovering from abdominal and orthopaedic surgery (Paymaster, 1976, 1977) the frequency of nausea and vomiting after meptazinol was not significantly different from that following pethidine or pentazocine. No psychotomimetic effects were observed after meptazinol, and the absence of euphoric or dysphoric effects is encouraging, particularly in view of the low physical dependence potential shown in animals (Goode and White, 1971; Swain, Villancal and Seevers, 1973).

The results of this study, and observations made in clinical studies, suggest that meptazinol has significant advantages over the currently available opiate analgesics.

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COMPARAISON DES EFFETS RESPIRATOIRES DU MEPTAZINOL, DE LA PENTAZOCINE ET DE LA MORPHINE

RESUME

Les effets respiratoires d'un nouvel analgésique puissant: le meptazinol, ont été comparés à un placebo et à des doses équianalgésiques de morphine et de pentazocine au cours d'une étude à double inconnue avec inversion des séries à la fin de la première période, effectuée sur six volontaires en bonne santé. On n'a observé aucune variation importante dans la réaction ventilatoire à la re-respiration de gaz carbonique après le meptazinol (100 mg 70 kg^{-1}) ou le placebo. Cependant, aussi bien la morphine (10 mg 70 kg^{-1}) que la pentazocine (60 mg 70 kg^{-1}) ont fait baisser la pente de la réaction ventilatoire (−30,0% et −31,6% respectivement, $P<0{,}02$, moyenne sur la première période de 3,5 h). La tension du gaz carbonique en fin d'expiration ($P_{E'_{CO_2}}$) a augmenté d'une manière significative après les trois médicaments, pendant que les volontaires respiraient l'air ambiant. L'augmentation de la $P_{E'_{CO_2}}$ après l'administration de meptazinol (0,22 kPa, moyenne sur 3,5 h) a été nettement inférieure à celle qui a suivi la morphine (0,40 kPa, $P<0{,}05$) et la pentazocine (0,59 kPa, $P<0{,}01$). Alors que les volontaires respiraient l'air ambiant avec une charge inspiratoire résistive de 8 kPa litre^{-1} s, la $P_{E'_{CO_2}}$ a à nouveau augmenté d'une manière significative ($P<0{,}05$) après les trois médicaments. L'augmentation de la $P_{E'_{CO_2}}$ après le meptazinol a alors été la même que celle qui a suivi la morphine (0,51 kPa, moyenne sur 3,5 h). L'augmentation qui a suivi la pentazocine (0,80 kPa) a été nettement plus grande que celle qui a suivi la morphine et le meptazinol ($P<0{,}02$).

VERGLEICH DER AUSWIRKUNGEN AUF DIE ATMUNG VON MEPTAZINOL, PENTAZOCIN UND MORPHIUM

ZUSAMMENFASSUNG

Die Auswirkungen eines starken neuen Analgeticums, Meptazinol, auf die Atmung wurden mit einem Plazebo und mit gleichwirksamen Dosen von Morphium und Pentazocin in einem Doppelblind-Kreuzversuch an 7 gesunden Versuchspersonen verglichen. Nach 100 mg/70 kg Meptazinol wurde keine wesentliche Anderung der Atmungsreaktion auf die Wiedereinatmung von Kohlendioxyd beobachtet, auch nicht nach Plazebo. Aber sowohl 10 mg/70 kg Morphium und 60 mg/70 kg Pentazocin unterdruckten die Belüftungsreaktion (−30,0% und −31,6%, $P<0{,}02$. Durchschnittlich über den ersten Abschnitt von 3,5 Studen). Die Endausatmungs-Kohlendioxydspannung ($P_{E'_{CO_2}}$) steig nach allen drei Drogen deutlich an, während Zimmerluft geatmet wurde. Aber der Anstieg dieses Wertes nach Meptazinol (0,22 kPa Durchschnitt uber 3,5 Stunden) war wesentlich geringer als nach Morphium (0,40 kPa, $P<0{,}05$) und nach Pentazocin (0,59 kPa, $P<0{,}01$). Bei normaler Luftatmung bei Einatmungsbelastung von 8 kPa litre^{-1} s stieg dieser Wert wieder stark an ($P<0{,}05$), nach allen drei Drogen. Der Anstieg nach Meptazinol war derselbe wie nach Morphium (0,51 kPa Durchschnitt über 3,5 Stunden). Der Anstieg nach Pentazocin (0,80 kPa) war deutlich grosser als nach Morphium oder Meptazinol ($P<0{,}02$).

COMPARACION DE LOS EFECTOS RESPIRATORIOS DEL MEPTAZINOL, DE LA PENTAZOCINA Y DE LA MORFINA

SUMARIO

Se procedío a la comparación de los efectos respiratorios de un nuevo analgésico fuerte, el meptazinol, con los de un placebo y con unas dosis equianalgésicas de morfina y de pentazocina en una prueba de traspaso ciega doble en siete voluntarios sanos. No se observó ningún cambio significativo en la respuesta ventilatoria al respirar de nuevo el dióxido de carbono, después de la administración de 100 mg 70 kg^{-1} de meptazinol o de placebo. Sin embargo, después de la administración de 100 mg 70 kg^{-1} de morfina y de 60 mg 70 kg^{-1} de pentazocina, el declive de la respuesta ventilatoria se deprimío ($-30{,}0\%$ y $-31{,}6\%$, respectivamente, $P < 0{,}02$, promediado sobre el primer perido de 3,5 h). La tensión respiratoria terminal del dióxido de carbono (PE'_{CO_2}), al respirar el aire del cuarto, subió de manera significativa después de las tres drogas. Sin embargo, el aumento del PE'_{CO_2} después del meptazinol (0,22 kPa, promediado sobre 3,5 h) era mucho menor que después de la morfina (0,40 kPa, $P < 0{,}05$) y de la pentazocina (0,59 kPa, $P < 0{,}01$). Mientras respiraban el aire del cuarto con una carga inspiratoria resistiva de 8 kPa $litre^{-1}$ s, el PE'_{CO_2} aumentó de nuevo significativamente ($P < 0{,}05$) después de la tres drogas. El incremento del PE'_{CO_2} después del meptazinol era entonces el mismo que después de la morfina (0,51 kPa promediado sobre 3,5 h). El aumento que siguió a la pentazocina (0.80 kPa) era mucho mayor que después de ambos productos: morfina y meptazinol ($P < 0{,}02$).

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PATTERN OF RESPIRATION AND RESPONSES TO CARBON DIOXIDE DURING TRICHLOROETHYLENE ANAESTHESIA IN THE CAT

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SUMMARY

Tidal volume (V_T), minute ventilation ($\dot{V}_E$), the duration of inspiration and expiration, and Pa_{CO_2} were measured via a tracheostomy in adult cats anaesthetized with 0.7%, 1% and 1.5% (inspired) trichloroethylene (TCE). The tracheal cannula was occluded at intervals at the start of inspiration and the tracheal pressure was measured to assess the force of contraction of the respiratory muscles. Anaesthesia with TCE 0.7% was associated with an increase in $\dot{V}_E$, a reduction in V_T, and a marked increase in respiratory frequency and mean inspiratory flow rate, but Pa_{CO_2} values did not differ significantly from those in conscious animals. Ventilation was also greater than in conscious animals during anaesthesia with TCE 1%. TCE 1.5% caused a significantly greater Pa_{CO_2} than in conscious animals. All concentrations of TCE caused a reduction in the ventilatory response to carbon dioxide, measured by the steady-state method. Cervical vagal section did not abolish the tachypnoea caused by TCE.

The characteristic pattern of breathing during anaesthesia with trichloroethylene (TCE) is a reduction in tidal volume (V_T) and an increase in respiratory frequency (f). Although this pattern has been known for many years (Hewer and Hadfield, 1941; Dundee, 1953), information about the effect of TCE on the pattern of respiration and the ventilatory response to carbon dioxide is sparse and often conflicting.

Whitteridge and Bülbring (1944) suggested that TCE caused a persistent sensitization of the inflation and deflation receptors in the cat lung and this could account for the reduction in tidal volume and tachypnoea seen during TCE anaesthesia. However, section of the vagi did not prevent the onset of tachypnoea after inhalation of TCE in decerebrate cats (Ngai, Katz and Farhie, 1965), suggesting that TCE causes this effect by a central action. Talcott, Larson and Buechel (1965) reported that TCE did not influence the ventilatory response to carbon dioxide in man, but the response was severely depressed in cats (Ngai, Katz and Farhie, 1965).

We have studied the effects of TCE anaesthesia on the pattern of breathing in adult cats. In addition to measurements of minute ventilation ($\dot{V}_E$), f and V_T, we measured the volume inspired in the first 0.1 s of inspiration ($V_{0.1}$), and the duration of inspiration, expiration and the total respiratory cycle (T_I, T_E and T_{tot} respectively). We calculated the mean inspiratory flow rate (V_T/T_I) and the ratio of inspiratory to total cycle duration (T_I/T_{tot}).

We occluded the airway at the onset of inspiration and measured the pressure change in the first 0.1 s of an inspiratory effort ($P_{0.1}$) (Whitelaw, Derenne and Milic-Emili, 1975). This pressure change indicated the tension generated by the inspiratory muscles. The occlusion was performed with the lung filled to functional residual capacity, and no flow of gas or change of volume occurred during the measurement (apart from the negligible decompression of gas in the lungs). Consequently, the dimensions of the respiratory system were nearly constant, and the magnitude of the tension developed in the respiratory muscles during isometric contraction had a consistent proportion to the degree of neural activation of these muscles. In this way, $P_{0.1}$ was used as an index of the rate of increase of activity of inspiratory motoneurones, or central inspiratory activity (Bradley et al., 1975; Eldridge, 1975). $V_{0.1}$ and V_T/T_I also indicate the rate of increase of inspiratory activity but they may be affected by changes in flow resistance or elastance (impedance) of the respiratory system (Whitelaw, Derenne and Milic-Emili, 1975). The relationship between $P_{0.1}$ and $V_{0.1}$ indicates changes in the

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mechanical properties of the respiratory system. For example, a reduction in $V_{0.1}$ may be caused by an increase in flow resistance or elastance of the respiratory system, in addition to a reduction in the rate of increase of activity of respiratory motoneurones or by neuromuscular impairment. An increase in the ratio $P_{0.1}/V_{0.1}$ would suggest that impedance had increased.

The ratio $T_{\mathrm{I}}/T_{\mathrm{tot}}$ indicates the fraction of time in which the inspiratory muscles are active. It has been called the "duty cycle" of the inspiratory muscles.

Ventilation, mean inspiratory flow and $T_{\mathrm{I}}/T_{\mathrm{tot}}$ can be related:

$$\dot{V}\mathrm{E} = V\mathrm{T}/T_{\mathrm{I}} \times T_{\mathrm{I}}/T_{\mathrm{tot}} \qquad (1)$$

The advantage of expressing ventilation in this way is that the first component ($V\mathrm{T}/T_{\mathrm{I}}$) is related only to the increasing activity of the inspiratory muscles and the second only to the proportional timing of the events in the respiratory cycle. This is not so for the conventional relationship:

$$\dot{V}\mathrm{E} = V\mathrm{T} \times 1/T_{\mathrm{tot}} \qquad (2)$$

because $V\mathrm{T}$ depends upon both the rate of inspiratory flow and the duration of inspiration. Euler, Herrero and Wexler (1970) proposed that changes in ventilation could be analysed in terms of the rate of increase in lung volume and mechanisms responsible for the timing of events of the respiratory cycle, since these appeared to be controlled separately.

METHODS

Adult cats (six non-pregnant females and three males) were premedicated with atropine 0.6 mg s.c. Previous experiments had shown that atropine 0.6 mg i.v. did not modify the respiratory pattern of cats anaesthetized with either halothane or pentobarbitone. Anaesthesia was induced with TCE 2% in 50% oxygen in nitrogen using a mask connected to a T-piece system with a gas flow rate of 8 litre min^{-1}. TCE was vaporized using a recently calibrated Tritec Mark 3 vaporizer (Cyprane Ltd). After 15–20 min a tracheal cannula was ligated firmly in the caudal part of the trachea and a femoral artery was cannulated. In five cats both vagi were dissected free in the neck and placed in loose ligatures to facilitate subsequent section.

The cat lay supine in a volume displacement body plethysmograph (Emerson) which had a linear response at frequencies less than 7 Hz. Tracheal pressure (from a sidearm in the tracheal cannula) and systemic arterial pressure were measured with Hewlett-Packard 267B and Statham P23AC transducers respectively and recorded with the volume signal on a Honeywell oscillograph. TCE was given by a T-piece connected to the tracheal cannula and the gas flow kept at three times the minute volume of the cat. The deadspace volume of the system from the tracheal cannula to the T-piece was 4 ml.

Arterial $P\mathrm{CO}_2$ was measured by taking two 1-ml samples from the arterial cannula, and analysing each in duplicate with a Corning 165 blood-gas analyser. Pa_{CO_2} was calculated as the mean of the four values (the mean absolute difference between the paired values was 0.18 kPa).

After preparation of the cat, which took about 1 h, any chosen TCE concentration was given for 60 min before measurements were made. Nine cats were studied with TCE 0.7%, five with 1% and two with TCE 1.5%. In the six cats in which more than one

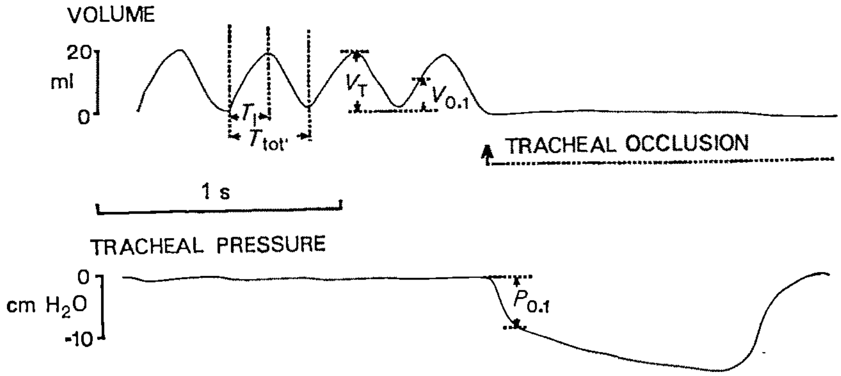

FIG. 1. A typical record of volume (upper trace) and tracheal pressure (lower trace) showing controls and an occluded breath, indicating the variables measured. The period of tracheal occlusion is indicated.

concentration was used, the concentration was increased in three and decreased in the other three.

At each TCE concentration, Pa_{CO_2} was measured and the airway was occluded on five occasions over a period of 2 min. Occlusion was performed at end-expiration, for the duration of one cycle of respiratory attempts, with at least 15–20 normal breaths between occlusions. Previous experiments had shown that the occlusions did not cause any change in the subsequent respiratory pattern or in Pa_{CO_2}. Tidal volume, the duration of inspiration and expiration, $V_{0.1}$ and $P_{0.1}$, were measured as appropriate from the three breaths preceding each occlusion and the first occluded respiratory effort (fig. 1). $\dot{V}_E$ and V_T/T_I were calculated for each breath and the mean of all values calculated for the whole period.

These five occlusions were repeated after two concentrations of carbon dioxide (first 2–3% and then 4–6%) had been added to the carrier gas for 5 min to allow the response to carbon dioxide to be measured at each TCE concentration.

Cervical section of the vagi was made in three cats breathing TCE 0.7% and in two cats breathing TCE 1%. Twenty minutes later the carbon dioxide response

TABLE I. *Mean and SD of respiratory variables in awake cats (Gautier, 1976) (A); cats anaesthetized with TCE* 0.7% *(B); and cats anaesthetized with TCE* 1% *(C). P values are given for comparison of groups A with B and B with C*

	Wt. (g)	$\dot{V}_E$ (ml min^{-1})	V_T (ml)	T_I (s)	T_{tot} (s)	Freq. (b.p.m.)	V_T/T_I (ml s^{-1})	T_I/T_{tot}	$V_{0.1}$ (ml)	$P_{0.1}$ (cm H$_2$O)	P_{max} (cm H$_2$O)	Pa_{CO_2} (kPa)
A ($n = 11$)												
Mean	3113	781	27.2	0.91	2.11	28.7	30.0	0.43	—	—	—	4.31
SD	505	167	5.0	0.05	0.20	3.3	6.2	0.05				0.23
B ($n = 9$)												
Mean	3446	2596	16.9	0.20	0.40	156.7	90.0	0.49	11.3	5.8	8.4	3.95
SD	453	453	2.6	0.05	0.09	37.3	20.2	0.05	1.6	1.0	2.3	0.70
P	n.s.	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.025				n.s.
C ($n = 5$)												
Mean	2592	1732	15.9	0.28	0.57	110.2	57.3	0.50	7.4	4.1	8.0	4.92
SD	402	337	1.2	0.06	0.13	26.1	11.4	0.02	1.4	0.6	0.8	0.62
P	n.s.	<0.005	n.s.	<0.025	<0.025	<0.05	<0.01	n.s.	<0.001	<0.005	n.s.	<0.025

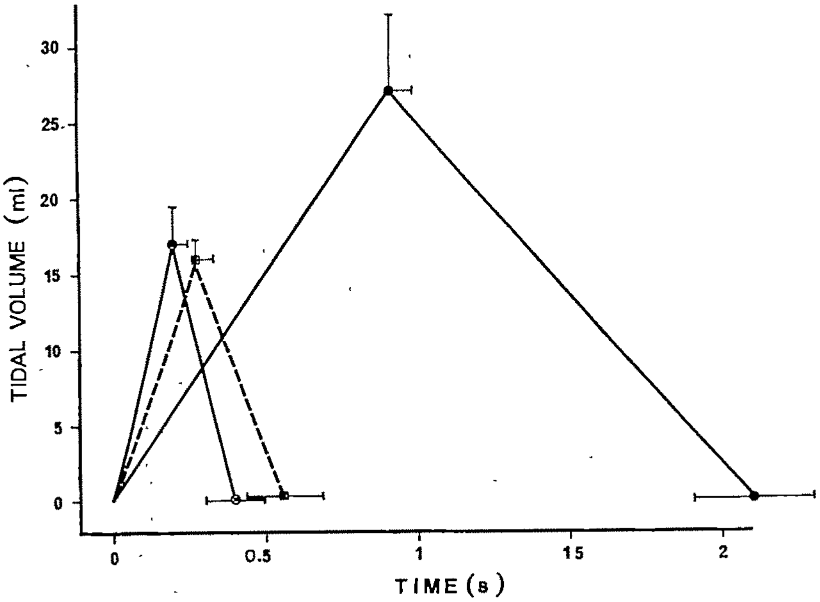

FIG. 2. Schematic spirograms using mean values (± SD) from table I for cats awake (closed circles) and during anaesthesia with TCE 0.7% (open circles), and TCE 1% (open squares).

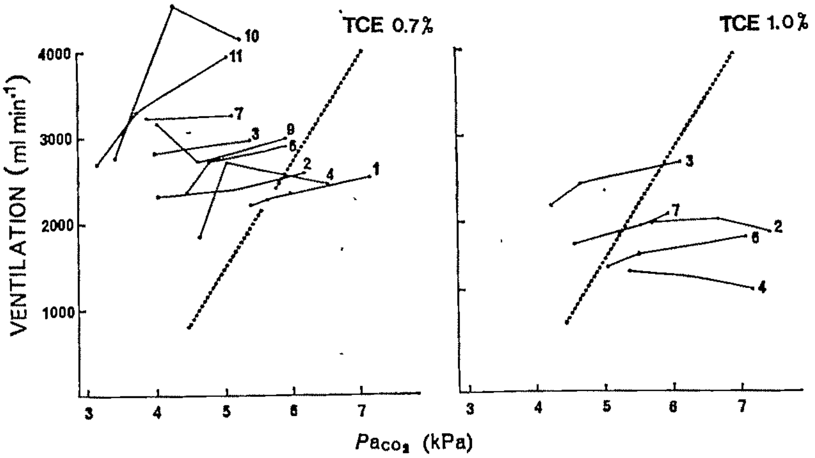

FIG. 3. Relationship of ventilation with arterial $P\text{CO}_2$ in individual cats anaesthetized with TCE 0.7% and 1%. Each cat is indicated by a reference number. The broken line represents the mean response of awake cats (Gautier, 1976).

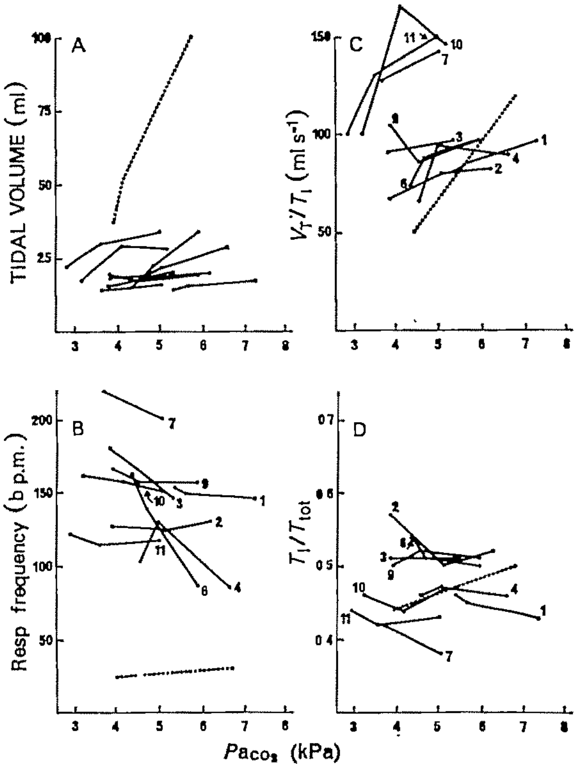

FIG. 4. Relationship of tidal volume, respiratory frequency, V_T/T_I and T_I/T_{tot} with Pa_{CO_2} in individual cats anaesthetized with TCE 0.7%. The broken lines represent the mean response of awake cats (Gautier, 1976).

was measured again. An aqueous solution of sodium chloride 0.9% was infused into the artery at a rate of 5 ml h⁻¹ for the duration of the experiment (4–6 h) and sampled blood was replaced with twice the volume of the saline solution.

Statistical analysis was made with Student's *t* test for paired and unpaired data as appropriate.

RESULTS

The mean values of the measured and derived variables for cats breathing TCE 0.7% and 1% in 50% oxygen are shown in table I, with similar data for conscious adult cats breathing air, studied by H. Gautier (personal communication). The weights of the groups were comparable. When compared with cats breathing air, the cats breathing TCE 0.7% had a greater $\dot{V}_E$, a smaller V_T and a markedly greater frequency. The mean rate of inspiration (V_T/T_I) was greater in proportion to the greater ventilation and T_I/T_{tot} was slightly but statistically significantly greater. Pa_{CO_2} was less but this was not statistically significant. The cats breathing TCE 1% had V_T similar to those breathing 0.7%, but T_I and T_{tot} were greater. Consequently $\dot{V}_E$ and V_T/T_I were less, T_I/T_{tot} was not significantly different, and Pa_{CO_2} was greater than in cats breathing TCE 0.7%. These differences are shown in figure 2, in which spirograms have been drawn using the mean values from table I.

In the two cats studied during anaesthesia with TCE 1.5%, ventilation was less than in the 1% group but V_T was about the same. Mean $\dot{V}_E$ was 1546 ml

min^{-1}, V_T was 15.5 ml and Pa_{CO_2} was 15.5 kPa.

The ventilatory responses to carbon dioxide for the individual cats in the TCE 0.7% and 1% groups are shown in figure 3, where the mean response of conscious cats is given for comparison (Gautier, 1976). In the cats breathing TCE 0.7%, the increase in $\dot{V}_E$ as Pa_{CO_2} was increased was much less than in awake animals. Two animals (Nos 4 and 10) showed an increase and then a reduction in $\dot{V}_E$ as the inhaled concentration of carbon dioxide was increased. The response to Pa_{CO_2} was even less in the TCE 1% group. No response to carbon dioxide was seen in the two animals breathing TCE 1.5%.

The influence of Pa_{CO_2} on V_T, f, V_T/T_I and T_I/T_{tot} is shown in figure 4 for cats breathing TCE 0.7%, and compared with data for conscious cats. The small increase in $\dot{V}_E$ was associated with an increase in V_T/T_I and V_T in all the animals, but f decreased in seven of the nine animals as Pa_{CO_2} increased, and T_I/T_{tot} decreased in five. In the cats breathing TCE 1% the changes were less consistent and no clear pattern was evident to account for the small increase in $\dot{V}_E$ that occurred with increased carbon dioxide in three of the five animals.

Before carbon dioxide was given, both $V_{0.1}$ and $P_{0.1}$ were less in the 1% than in the 0.7% group. The difference was greater for $V_{0.1}$, but the ratio $P_{0.1}/V_{0.1}$ was not significantly greater than in the TCE 1% group. No change in the ratio of $P_{0.1}/V_{0.1}$ occurred with the increase in Pa_{CO_2} at any of the inhaled TCE concentrations.

Vagotomy. Bilateral section of the vagi in the neck in three animals breathing TCE 0.7% (table II) and in two animals breathing TCE 1% did not cause a significant change in $\dot{V}_E$, but T_I and V_T increased and frequency was reduced. However, only the change in V_T in the TCE 0.7% group was significant using the paired t test ($P<0.05$). V_T/T_I and T_I/T_{tot} did not change. The changes in the spirogram are illustrated in figure 5 for the TCE 0.7% group. Pa_{CO_2} decreased in all animals, except one breathing TCE 0.7%. The ventilatory response to carbon dioxide was characterized by an increase in V_T as Pa_{CO_2} was increased. However, $\dot{V}_E$ increased in only three animals when Pa_{CO_2} was increased (two breathing TCE 0.7%, and one breathing TCE 1%) and was associated with an increase in V_T/T_I. The changes in timing of respiration that occurred with increasing Pa_{CO_2} did not show a consistent pattern.

Vagal section did not influence mean arterial pressure which remained greater than 100 mm Hg throughout the experiment.

DISCUSSION

Choice of species. We studied cats because there is a large amount of previous experimental work on their

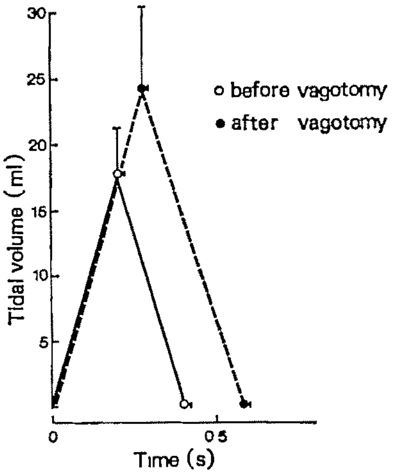

FIG. 5. Schematic spirogram using mean values (±SD) from cats 3, 10 and 11 before (open circles) and after vagotomy (closed circles), anaesthetized with TCE 0.7%. Comparison of the spirogram after vagotomy with that of awake animals in figure 2 shows that the tachypnoea was not abolished by vagal section.

TABLE II. *Respiratory variables before (I) and after (II) vagotomy in cats anaesthetized with TCE 0.7%. P values are for paired t test before and after vagotomy*

Cat no.		$\dot{V}_E$ (ml min^{-1})	V_T (ml)	T_I (s)	T_{tot} (s)	Freq. (b.p.m.)	V_T/T_I (ml s^{-1})	T_I/T_{tot}	$V_{0.1}$ (ml)	$P_{0.1}$ (cm H_2O)	P_{max} (cm H_2O)	Pa_{CO_2} (kPa)
3	I	2817	15.5	0.17	0.33	182	91	0.51	11.6	7.0	10.5	3.8
	II	2496	20.8	0.28	0.50	120	74	0.56	11.6	7.4	10.5	2.9
10	I	2522	16.4	0.17	0.37	162	96	0.44	13.1	5.7	6.7	3.2
	II	2675	21.4	0.20	0.44	136	86	0.52	12.4	4.4	6.0	4.1
11	I	2692	22	0.22	0.49	122	100	0.44	14.3	4.8	5.4	2.9
	II	2492	32	0.31	0.77	78	103	0.40	18.3	6.1	6.8	2.8
P		n.s.	<0.05	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.

pattern of respiration in the awake and anaesthetized states. In addition previous authors have reported effects of TCE in this species (Whitteridge and Bülbring, 1944; Ngai, Katz and Farhie, 1965; Coleridge et al., 1968). The slow onset and prolonged recovery from stable TCE anaesthesia in man would have made this study difficult to perform in clinical circumstances.

Widdicombe (1961) suggested that the reflex inhibition of inspiration by lung inflation (Hering–Breuer reflex) was weak in man and relatively weak in the cat, in comparison with other animal species. However, this method of assessment of the strength of the Hering–Breuer reflex has been shown to be misleading (Younes, Vaillancourt and Milic-Emili, 1974). Clark and Euler (1972) showed that the responses of cat and man were similar, although the reflex is not present in man in the eupnoeic range of breathing (Guz et al., 1964).

Methods. The cats were allowed to breathe the appropriate concentration of TCE for 60 min before measurements were made. We consider that this was sufficient to achieve a stable brain concentration of anaesthetic. Measurement of end-expiratory concentrations of trichloroethylene was not possible because of tachypnoea and small tidal volumes. In trial experiments, the inhaled concentration was reduced to 0.5% after at least 1 h of anaesthesia with TCE 0.7%. Coughing and other reflex activity occurred within 10 min of this reduction, and attempts to study cats using this concentration were abandoned. These observations suggested that the change of brain concentration was rapid, possibly because of hyperventilation, and that 1 h would be an appropriate time to allow stabilization. The brain concentration of TCE could have been increased during carbon dioxide administration by an increase in ventilation and possibly in cerebral blood flow. This could account for the increase followed by a decrease in ventilation seen in two cats after inhalation of carbon dioxide. Alternative explanations would be a direct depressant effect of carbon dioxide or fatigue of the respiratory muscles.

Gabbard and others (1952) observed a similar reduction in ventilation at greater Pa_{CO_2} values in human subjects anaesthetized with ether.

Ventilation. Our results show that ventilation was much greater during inhalation of TCE 0.7% than in unanaesthetized animals. Although the respiratory frequency was markedly greater the relative duration of inspiration in the total respiratory cycle was not greatly increased, because T_I/T_{tot} was 0.49 during TCE 0.7% anaesthesia, and 0.43 in awake cats. Consequently the rate of inspiration also had to be greater, and in fact V_T/T_I was 200% greater during TCE 0.7% anaesthesia than in the conscious animals. It is most unlikely that this could have been caused by altered mechanics of the respiratory system, so that the greater flow rate must have been the result of a more rapid contraction of the respiratory muscles, caused by an increase in the rate of activation of respiratory motoneurones. Therefore TCE causes increased activity of these motoneurones. This conclusion is contrary to the opinion that TCE stimulates respiration by an increase in frequency alone (Severinghaus and Larson, 1965) and illustrates an advantage of considering ventilation in terms of the mean flow and relative duration of inspiration. In the cat, other respiratory stimulants such as caffeine (Mazzarelli, unpublished observations) and doxapram (Bopp, Drummond and Milic-Emili, unpublished observations) have been shown to act by increasing V_T/T_I, and respiratory depressants such as enflurane (Mazzarelli, Chiolero and Milic-Emili, 1979) by decreasing V_T/T_I. In the present study, greater inhaled concentrations of TCE were associated with smaller values of V_T/T_I. Greater inhaled concentrations were not associated with an increase in tachypnoea as has been suggested for man (Dundee, 1953). On the contrary, frequency was less, although T_I/T_{tot} was not different.

The efficiency of ventilation was reduced markedly, presumably by tachypnoea. Ventilation during inhalation of TCE 0.7% was more than three times that in conscious animals, whereas Pa_{CO_2} values were not significantly different in the two states.

Pa_{CO_2} values agree with values reported in clinical studies (Talcott, Larson and Buechel, 1965; Unni, McArdle and Dundee, 1972; Buchan and Bauld, 1973). Marked hypercapnia was present only during anaesthesia with TCE 1.5%, presumably because of an inefficient pattern of respiration.

Diethyl ether is the only other agent that causes an increase in ventilation and a marked increase in frequency (Larson et al., 1969), but no information is available on the respiratory pattern during ether anaesthesia, except in newborn rabbits. Tachypnoea occurs also, but the slight increase in ventilation is caused entirely by an increase in T_I/T_{tot} (Thatch, Wyszogrodski and Milic-Emili, 1976).

Vagotomy. Statistically significant results were not obtained after vagotomy because only a limited number of cats was studied. The most important finding was that tachypnoea was not abolished. Ventilation was essentially unchanged. V_T increased significantly and frequency decreased, but this change was not significant statistically. The more efficient pattern of ventilation resulted in a decrease in Pa_{CO_2} in four of the five animals studied. Vagotomy did not seem to influence V_T/T_I and T_I/T_{tot}. The ratio of $P_{0.1}$ to $V_{0.1}$ (effective impedance) did not change markedly, so the mechanical properties of the respiratory system did not appear to be altered.

Whitteridge and Bülbring (1944), using cats after spinal section, showed that the discharge of pulmonary stretch receptors was increased by 30–50% during brief ventilation with TCE 0.5–1%. This finding was confirmed in intact cats anaesthetized with either chloralose or pentobarbitone by Coleridge and others (1968) who also showed that TCE 1% did not influence the activity of "high threshold receptors" whose impulses were conducted at mean velocities of 1.5 m s^{-1}. Sensitization of pulmonary stretch receptors has been suggested to account for tachypnoea during anaesthesia with TCE and other agents, in animals and man. However, Ngai, Katz and Farhie (1965) showed that TCE caused tachypnoea in cats after vagotomy. Lung inflation does not cause increased tachypnoea in patients anaesthetized with halothane, methoxyflurane or fluroxene as would be expected if the tachypnoea were caused by an active expiration promoting Hering–Breuer reflex (Paskin, Skovsted and Smith, 1968). Vagal section in dogs anaesthetized with ether (Muallem, Larson and Eger, 1969) and in cats during halothane administration (Younes and Yousef, 1978) did not prevent tachypnoea.

The ratio of total cycle duration before and after vagotomy in the present study was about the same as would be predicted on the basis of the relationship of this ratio to tidal volume, as described by Grunstein, Younes and Milic-Emili (1973) in a study of cats anaesthetized with pentobarbitone.

The cats in the present study had respiratory rates between 100 and 160 b.p.m. In decerebrate cats given TCE 1% the respiratory rate was increased to only 50 b.p.m. and vagal section and carotid denervation did not influence the ability of TCE to cause tachypnoea (Ngai, Katz and Farhie, 1965). The greater respiratory rates in the present study suggest that TCE may cause tachypnoea by action at a site proximal to the brain-stem colliculi, possibly in the way that hyperthermia causes tachypnoea (Pitts, Magoun and Ranson, 1939), or even proximal to the diencephalon (Cohen, 1964).

These findings support the analogy drawn by Ngai (1968), who pointed out that although baroreceptors are sensitized by anaesthetics, this is not responsible for hypotension during anaesthesia. An increase in vagal afferent activity may occur during TCE administration, but the response of the central mechanisms seems to be reduced so that the end result of vagal activity seems similar to that seen in other forms of anaesthesia. Afferent impulses from the chest wall, such as muscle spindles, have been shown to influence the duration of inspiration (Remmers, 1970) and TCE may cause tachypnoea by augmenting such a reflex.

Ventilatory response to carbon dioxide. The study of Ngai, Katz and Farhie (1965) in decerebrate cats showed that the ventilatory response to carbon dioxide was reduced by TCE. On the other hand, Talcott, Larson and Buechel (1965) suggested that the mean ventilatory response of five human subjects was not influenced by anaesthesia using TCE 1 and 2%. However, the mean ventilatory response of the conscious subjects was small, and the range of increase in carbon dioxide values (0.4–0.8 kPa) was also small (Severinghaus and Larson, 1965). Our results show that the actions of TCE resemble those of ether, consisting of an increase in ventilation in the absence of stimulation with inhaled carbon dioxide but a reduced carbon dioxide response (Muallem, Larson and Eger, 1969). Many other volatile anaesthetic agents cause a decrease in ventilation and a reduced carbon dioxide response (Munson et al., 1966).

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MODELE DE RESPIRATION ET REACTIONS AU GAZ CARBONIQUE PENDANT UNE ANESTHESIE AU TRICHLOROETHYLENE CHEZ LE CHAT

RESUME

On a mesuré le volume courant (V_T), la ventilation par minute ($\dot{V}_E$), la durée de l'inspiration et de l'expiration, de même que la Pa_{CO_2} grace à une trachéotomie effectuée sur des chats adultes, anesthésiés au trichloroéthylène (TCE) inspiré à raison de 0,7%, 1% et 1,5%. La canule trachéale a été obturée à certains intervalles au début de l'inspiration et on a mesuré la pression trachéale pour estimer la force de contraction des muscles respiratoires. L'anesthésie à l'aide de TCE à 0,7% a été associée à une augmentation de la $\dot{V}_E$, à une réduction du V_T et à une augmentation marquée de la fréquence respiratoire et du taux moyen de débit inspiratoire, mais les valeurs de la Pa_{CO_2} n'ont pas différé d'une manière très significative de celles des animaux conscients. La ventilation a aussi été plus forte que sur les animaux conscients, pendant l'anesthésie à l'aide de TCE à 1%. Le TCE à 1,5% a provoqué une Pa_{CO_2} sensiblement plus grande que sur les animaux conscients. Toutes les concentrations de TCE ont causé une réduction de la réaction ventilatoire au gaz carbonique, mesurée à l'aide de la méthode de l'équilibre cinétique. La section cervicale vagale n'a pas empêché la tachypnée causée par le TCE.

ATMUNGSRHYTMUS UND REAKTIONEN AUF KOHLENDIOXYD WÄHREND EINER TRICHLOROÄTHYLEN-ANÄSTHESIE BEI KATZEN

ZUSAMMENFASSUNG

Atemvolumen, Minutenventilation, die Dauer von Ein- und Austamung, sowie Pa_{CO_2} wurden durch Tracheostomie bei Katzen gemessen, die durch die Einatmung von 0,7%, 1% und 1,5% Trichloroäthylen (TCE) narkotisiert waren. Die Trachealkanüle wurde gelegentlich zu Beginn der Einatmung okkludiert, und der Trachealdruck wurde gemessen, um die Kontraktionskraft der Atemmuskeln zu bewerten. Eine Narkose mit 0,7% TCE ergab einen Anstieg in $\dot{V}_E$,

eine Reduktion in V_T und einen deutlichen Ansteig von Atmungsfrequenz und mittlerer Einatmungsstromrate, doch unterschieden sich die Werte von Pa_{CO_2} nicht wesentlich von denen nichtnarkotisierter Tiere. Die Belüftung war auch bei Narkose mit 1% TCE grösser als bei nichtnarkotisierten Tieren. 1,5% TCE bewirkte einen deutlich höheren Wert von Pa_{CO_2} als bei nichtnarkotisierten Tieren. Alle Konzentrationen von TCE bewirkten eine Reduktion der Belüftungsreaktion auf Kohlendioxyd, gemessen durch die Gleichmassigkeitsmethode. Zervikale Vagal-Sektion eliminierte nicht die durch TCE verursachte Tachypnoe.

ESTRUCTURA DE LA RESPIRACION Y DE LAS RESPUESTAS AL DIOXIDO DE CARBONO DURANTE LA ANESTESIA POR TRICLOROETILENO EN EL GATO

SUMARIO

Mediante una traqueostomía en gatos adultos anestesiados por medio de 0,7%, 1% y 1,5% de tricloroetileno (TCE) inspirado, se midieron el volumen respiratorio (V_T), la ventilación por minuto ($\dot{V}_E$), la duración de la inspiración y de la expiración, así como el Pa_{CO_2}. Al principio de la inspiración, estaba ocluída a intervalos la cánula traqueal y se midió la presión traqueal para evaluar la fuerza de contracción de los músculos respiratorios. La anestesia mediante 0,7% de TCE se acompañó de un aumento de $\dot{V}_E$, una reducción del V_T y de un incremento marcado de la frecuencia respiratoria y del ritmo del flujo inspiratorio medio, pero los valores del Pa_{CO_2} no se alteraron de manera significativa para con los de animales conscientes. También era mayor la ventilación durante la anestesia con un 1% de TCE que la de los animales conscientes. Un 1,5% de TCE dió lugar a un Pa_{CO_2} sensiblemente mayor que en los animales conscientes. Todas las concentraciones de TCE provocaron una reducción de la respuesta ventilatoria al dióxido de carbono, medido según el método de estado estable. La sección vagal cervical no eliminó la taquínea causada por el TCE.

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HAEMODYNAMIC CONSEQUENCES OF CITRATE INFUSION IN THE ANAESTHETIZED DOG: COMPARISON BETWEEN TWO CITRATE SOLUTIONS AND THE INFLUENCE OF BETA BLOCKADE

L. J. Drop and D. Scheidegger

SUMMARY

We have compared the effects of a solution of acid–citrate–dextrose (ACD) with those of a solution of citrate–phosphate–dextrose (CPD), infused at equal rates, on blood calcium ion concentration and different indices of haemodynamic performance in 17 dogs. The influence of beta adrenergic blockade on these changes was examined. The effects of ACD and CPD were studied in five dogs and were similar. Peripheral vascular changes were the principal cause of arterial hypotension. In six dogs, propranolol 0.5 mg kg^{-1} intensified the hypocalcaemia-induced left ventricular dysfunction.

The rapid i.v. infusion of citrated whole blood can be associated with arterial hypotension (Denlinger and Nahrwold, 1976) as a result of a decrease in the concentration of calcium ion ($[Ca^{2+}]$) in the plasma (Cooper et al., 1973; Denlinger and Nahrwold, 1976; Olinger et al., 1976). This change in arterial pressure may be secondary to alterations in ventricular function or peripheral vascular function, or both. The blood preservatives which are used commonly contain either citric acid, trisodium citrate and dextrose (ACD) or trisodium citrate, citric acid, sodium phosphate and dextrose (CPD). In the blood transfusion service of the Massachusetts General Hospital, where between 30 000 and 40 000 units of whole blood are collected each year, ACD solution is used almost exclusively for blood preservation, primarily because of the technique employed to prepare platelet-rich plasma from donor blood for blood component therapy.

Although Hedley-Whyte and associates (1976) have suggested that the CPD solution may be a better alternative for blood preservation, experimental data have not been available to demonstrate its superiority in the maintenance of haemodynamic stability in the recipient of the blood.

Preliminary observations (Bunker, Bendixen and Murphy, 1962; Smith and Hurley, 1969) have suggested that the haemodynamic effects of citrate loading may be more pronounced in the presence of beta blockade. However, the magnitude of this interaction has not been established.

The present study was undertaken to compare the effects of an infusion of ACD solution with those of an infusion of CPD solution, administered at the same rate, upon $[Ca^{2+}]$ and haemodynamic function in the anaesthetized dog. In addition we sought to define the extent to which the haemodynamic consequences of transient hypocalcaemia may be modified by beta blockade.

METHODS

Seventeen mongrel dogs of either sex (weight range 18–21 kg) were anaesthetized with thiopentone 25 mg kg^{-1} i.v. followed by the spontaneous inhalation of halothane 0.9–1.1% in oxygen via a cuffed endotracheal tube. Catheters were placed in the femoral artery, right atrium and pulmonary artery (Edwards Laboratories). In all animals, a period of approximately 1 h elapsed between the administration of the thiopentone and the onset of the experiment. Core temperature was monitored using an oesophageal temperature probe (Yellow Springs Instruments) and did not vary by more than 0.5 °C from 37 °C in any animal.

Haemodynamic measurements

Femoral arterial, right atrial and pulmonary arterial pressures were recorded continuously (Hewlett Packard 7788 recorder and Sanborn 267 BC transducers). Mean pulmonary artery balloon-occluded pressure ($P\overline{PA}_0$), which was recorded at each measurement interval, was used to estimate left ventricular

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filling pressure; mean right atrial pressure ($P\overline{\text{RA}}_0$) was used to estimate right ventricular filling pressure. Mean pressures were obtained by electronic integration. Cardiac output (CO) was determined by thermodilution (Ganz and Swan, 1972). Lead II of the electrocardiogram was recorded to determine heart rate (HR). Systemic vascular resistance (SVR) was calculated according to a standard formula (Yang et al., 1972). The blood volume status of all animals was considered normal since oral intake had been unrestricted up to 1 h before the induction of anaesthesia and lactated Ringer's solution 1.5 ml kg^{-1} h^{-1} was administered i.v. throughout the experiment.

Whole blood measurements

Arterial blood samples were withdrawn for the determination of biochemical variables. The ionized calcium concentration ([Ca^{2+}]) was determined in heparinized specimens of whole blood (5 i.u. heparin per ml of whole blood) by a thermostatically controlled (37 °C) automated flow-through calcium-selective electrode system (Orion SS 20). The system was calibrated as described previously (Madsen and Olgaard, 1977; Drop, Fuchs and Stulz, 1978). Blood-gas tensions and pH were measured at 37 °C by the use of appropriate electrodes (Radiometer).

Plasma measurements

The total calcium concentration in plasma ([Ca]) was determined by EDTA titration using calcein as the indicator (Bett and Fraser, 1959), total protein by refractometry (Sunderman, 1944), and inorganic phosphorus (P_i) was determined as the phosphomolybdate by spectrophotometry (Chen, Toribara and Warner, 1956). The concentrations of sodium (Na^+) and potassium (K^+) and the osmolality were determined by standard methods.

Solutions

The ACD solution was prepared by adding trisodium citrate 14.37 g, citric acid 13.493 g and dextrose 24.4 g to distilled water to a final volume of 1 litre. The calculated citrate concentration was 127 mmol litre^{-1}. The CPD solution was prepared by adding trisodium citrate 11.493 g, citric acid 12.873 g, monobasic sodium phosphate 2.22 g and dextrose 25.56 g to distilled water to a final volume of 1 litre. The total citrate concentration in this solution was 111 mmol litre^{-1}. In both solutions, total citrate concentrations are those present in ACD and CPD solution formula A USP, but the proportions of trisodium citrate and citric acid were selected such that the concentration of Na^+ would range between 149 and 152 mmol litre^{-1}, and this was confirmed by flame photometry.

To study the effects citrate itself might have without a disturbance of calcium ion homeostasis, a solution of ACD was prepared as described, but the calcium ion concentration was titrated to approximately 1.10 mmol litre^{-1} by the addition of $CaCl_2$.

In all solutions, KCl was added to ensure a final K^+ concentration of 4 mmol litre^{-1} and pH was adjusted to 7.40 unit by the addition of TRIS buffer. These adjustments were necessary to avoid changes in any biochemical variable other than the one under study ([Ca^{2+}]).

Experimental programme

Group I ($n = 5$). Following control measurements, one randomly selected citrate solution (ACD or CPD) was infused i.v. at a rate of 1.5 ml kg^{-1} over a 30-s period. Haemodynamic measurements were made and arterial blood samples were withdrawn at 15 s and at 5-min intervals for up to 30 min following the termination of the infusion. Following a 30-min period, during which all the measured haemodynamic variables and [Ca^{2+}] had returned to their respective control values, the other citrate solution was infused at the same rate. Haemodynamic measurements were made and arterial blood specimens withdrawn as described.

Group II ($n = 6$). ACD solution 1.5 ml kg^{-1} was infused i.v. over a 30-s period and measurements made as described for group I. Following a 30-min period during which all the haemodynamic variables and [Ca^{2+}] had returned to their respective control values, beta blockade was instituted by the infusion of propranolol 0.5 mg kg^{-1} i.v. and confirmed by a lack of tachycardia following an isoprenaline challenge (0.9 μg kg^{-1} over 1 min). Following a 20-min period, ACD solution 1.5 ml kg^{-1} was infused again and measurements made as described in group I.

Group III ($n = 6$). To determine whether citrate *per se* or the volume infused might alter haemodynamic function, the ACD solution in which [Ca^{2+}] had been titrated to 1.10 mmol litre^{-1} was infused (1.5 ml kg^{-1}) and measurements made at the same time intervals as in group I.

Statistical evaluation of data

To determine the significance of the difference between the experimental data obtained in one group of animals Student's *t* test for paired data was applied. To determine the significance of the difference between data obtained in two groups of animals

Student's *t* test for unpaired data was applied. Values are expressed as mean ± SEM. Differences were considered significant if $P < 0.05$.

RESULTS

Effects of citrate

Following the infusion of ACD solution i.v. in which [Ca^{2+}] had been adjusted to the normal range, the measured and calculated haemodynamic variables and all biochemical variables remained unchanged. Thus the possibility of an effect of citrate *per se* or the volume of fluid infused could be excluded.

Effects of beta blockade

The haemodynamic effects of beta blockade were examined by comparing the data obtained at normal [Ca^{2+}] before institution of beta blockade with those after beta blockade was established. Following the onset of beta blockade, HR decreased (133 ± 3.2 *v.* 117 ± 3.2 beat min^{-1}; $P < 0.001$) as did CO (4.3 ± 0.39 litre min^{-1} *v.* 3.79 ± 0.39 litre min^{-1}; $P < 0.05$). $P\overline{PA}_0$ increased from 5.5 ± 0.6 to 7.2 ± 1.0 mm Hg; $P < 0.001$. The change in SVR was not significant.

ACD v. CPD

The haemodynamic variables measured before the infusion of ACD were not significantly different from those recorded before the infusion of CPD (figs 1, 2). The infusion of ACD was associated with a significant decrease in [Ca^{2+}] which was no longer significantly different from control at 30 min. The decrease in m.a.p. was significant up to 15 min. After a transient increase in CO recorded at 5 min, this variable was not different from control for the remainder of the

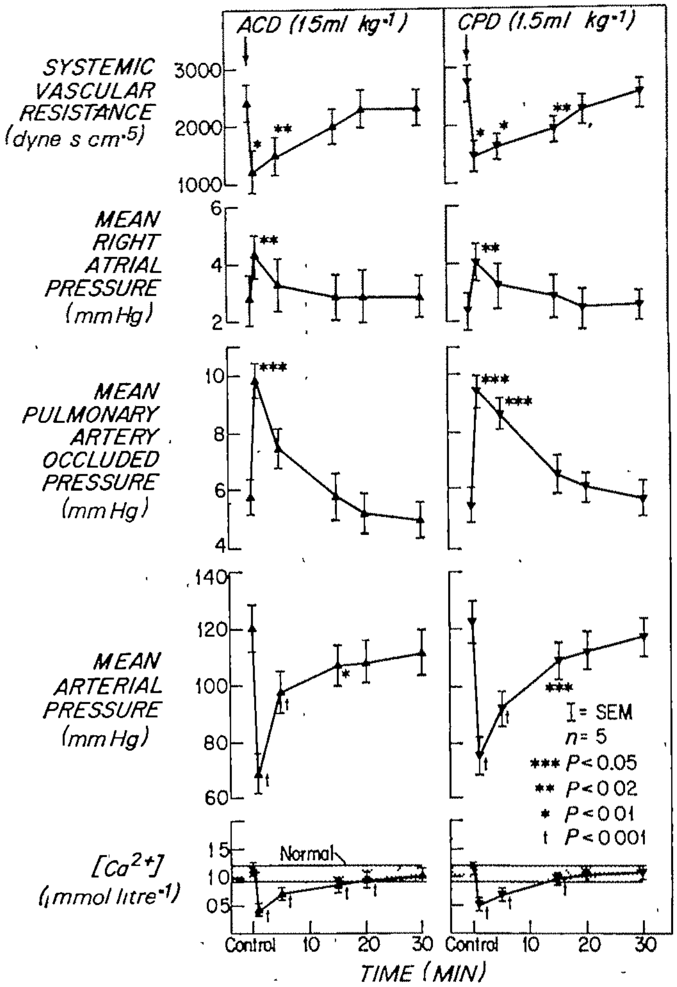

FIG. 1. Haemodynamic consequences of transient hypocalcaemia during halothane anaesthesia. Cardiac output either increased or remained unchanged while mean arterial pressure decreased. Thus decreased resistance in the systemic vasculature was the principal determinant of the decrease in m.a.p. The magnitude of these changes was independent of the type of citrate solution infused.

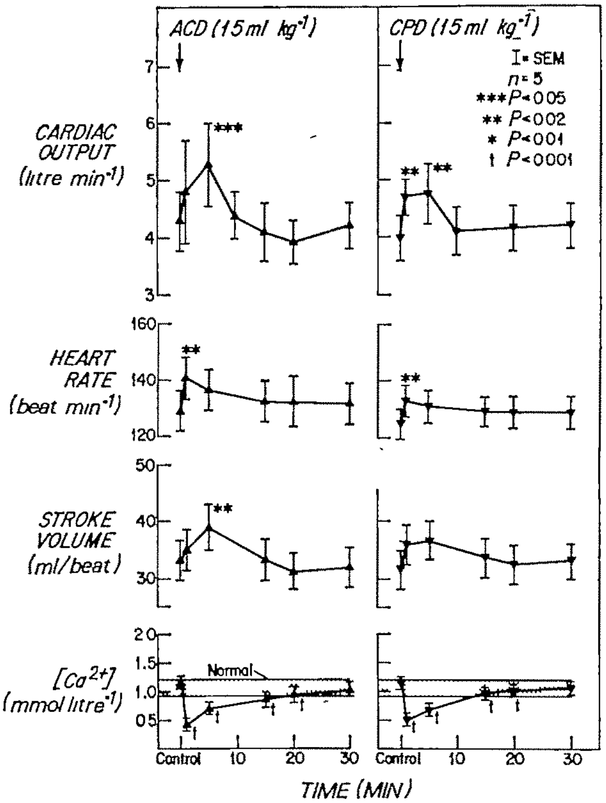

FIG. 2. Haemodynamic consequences of transient hypocalcaemia during halothane anaesthesia. M.a.p. decreased, while $P\overline{PA}_0$ increased (fig 1), with changes in CO and SV as noted here.

observation period. A significant increase in $P\overline{PA}_0$ was recorded 15 s following the infusion of citrate; changes in this variable were not significantly different from control thereafter. A decrease in SVR was noted up to the 5-min observation period. Increases in HR and $P\overline{RA}$ were present at 15 s only.

Following i.v. infusion of CPD solution, changes in [Ca^{2+}] and in measured and calculated haemodynamic variables were not different from those recorded following ACD infusion.

Influence of beta blockade on haemodynamic consequences of transient hypocalcaemia

Before beta blockade, CO and SV were greater than control 5 min following ACD infusion. However, these variables were not significantly different from control despite an increase in $P\overline{PA}_0$ and a decrease in m.a.p. at the corresponding time intervals when beta blockade was present (figs 3, 4).

Biochemical variables and arterial blood-gas tensions

The decrease in [Ca^{2+}] observed following the infusion of ACD was similar to that observed following the infusion of CPD. Values of Pa_{O_2}, Pa_{CO_2}, pH, [Ca], Na$^+$, K$^+$, total protein and P_i remained unchanged throughout the observation periods and were not influenced by the type of citrate solution infused. Thus a transient decrease in [Ca^{2+}] was not apparent from a change in [Ca] (table I).

DISCUSSION

The results obtained in this study demonstrate that two commonly employed blood preservatives have similar effects on [Ca^{2+}] and haemodynamic function despite a 12.5% difference in total citrate concentration. Although a decrease in [Ca^{2+}] was associated with changes in both ventricular and peripheral vascular function, the alteration in peripheral vascular function (a decrease in SVR) was the principal determinant of the decreased arterial pressure. In addition, the myocardial depressant effects of transient hypocalcaemia were accentuated in the presence of beta blockade.

Our data indicate that, despite a difference in total citrate concentration, the infusions of ACD and CPD

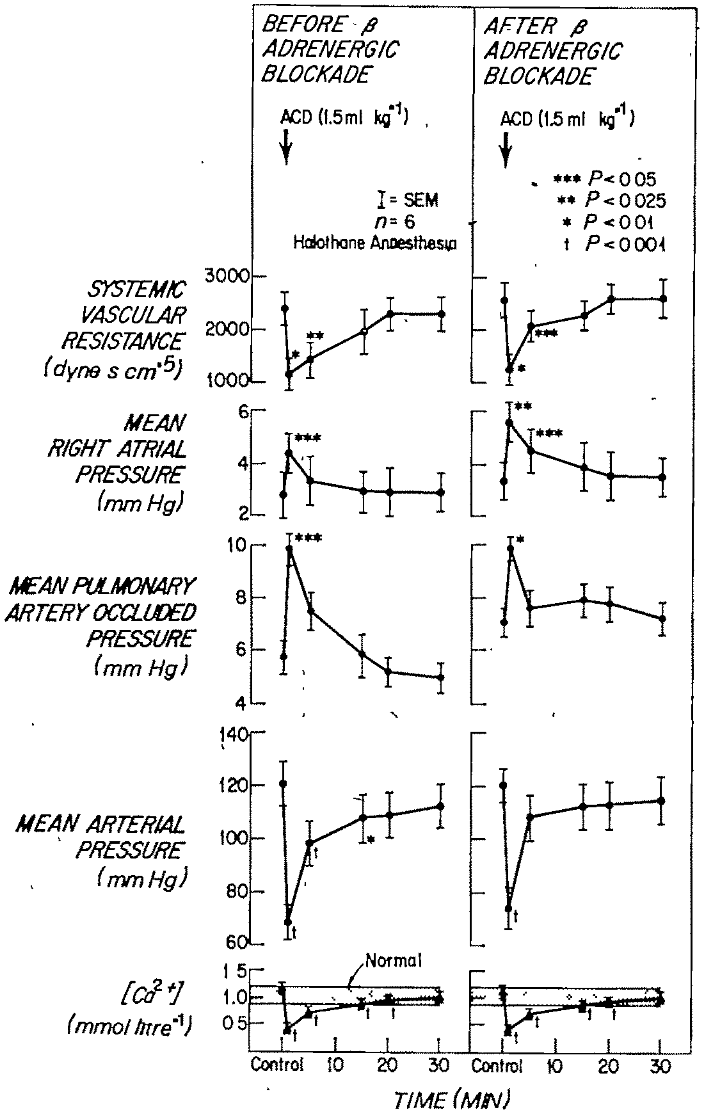

FIG. 3. Influence of beta blockade on haemodynamic consequences of citrate infusion during halothane anaesthesia. The variables shown were not significantly altered by beta blockade.

TABLE I. *Biochemical variables (mean ± SEM) during transient hypocalcaemia. Note that the disturbance in* [Ca^{2+}] *was not apparent from* [Ca] *measurements.* (* $P < 0.001$ *v. control*)

	ACD infusion				CPD infusion			
		After infusion (min)				After infusion (min)		
	Control	5	15	30	Control	5	15	30
[Ca^{2+}] (mmol $litre^{-1}$)	1.18 ± 0.03	0.74* ± 0.03	0.97* ± 0.02	1.15 ± 0.03	1.19 ± 0.05	0.71* ± 0.04	1.02* ± 0.02	1.15 ± 0.03
[Ca] (mmol $litre^{-1}$)	2.19 ± 0.08	2.13 ± 0.1	2.08 ± 0.08	2.16 ± 0.1	2.23 ± 0.1	2.19 ± 0.1	2.15 ± 0.25	2.20 ± 0.3
P_i (mmol $litre^{-1}$)	1.3 ± 0.2	1.3 ± 0.2	1.2 ± 0.2	1.2 ± 0.2	1.1 ± 0.3	1.2 ± 0.1	1.3 ± 0.3	1.3 ± 0.3
pH (unit)	7.38 ± 0.02	7.39 ± 0.02	7.39 ± 0.02	7.36 ± 0.01	7.36 ± 0.03	7.35 ± 0.03	7.36 ± 0.03	7.39 ± 0.02
Na^+ (mmol $litre^{-1}$)	146 ± 0.9	146 ± 1.0	145 ± 0.9	146 ± 0.9	142 ± 1.2	144 ± 1.2	144 ± 1.0	145 ± 1.2
K^+ (mmol $litre^{-1}$)	3.7 ± 0.3	3.6 ± 0.3	3.6 ± 0.2	3.6 ± 0.2	3.6 ± 0.2	3.6 ± 0.3	3.5 ± 0.3	3.5 ± 0.3

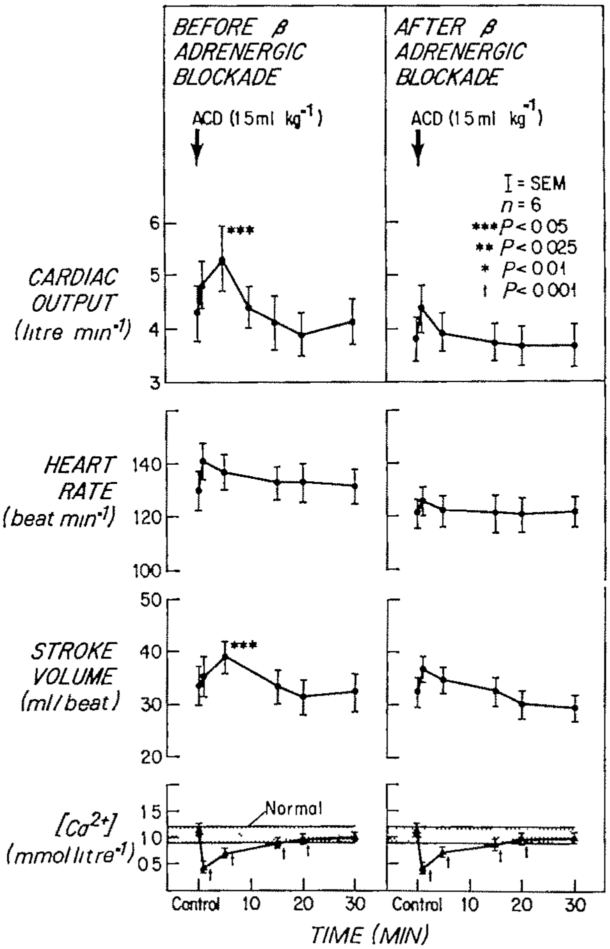

FIG. 4. Influence of beta blockade on haemodynamic consequences of citrate infusion during halothane anaesthesia. Before blockade, cardiac output and stroke volume increased significantly in response to decreased m.a.p. and increased $P\overline{PA}_0$ whereas, following blockade, alterations in CO and SV were insignificant despite decreased m.a.p. and increased $P\overline{PA}_0$.

in the intact animal were associated with similar alterations in [Ca^{2+}] homeostasis and haemodynamic function. We infused citrate solutions in which the citrate concentration was exactly that present in the solutions used for blood preservation as formulated in the Technical Manual of the American Association of Blood Banks (Miller, 1977). However, adjustments of [Na^+], [K^+] and pH were made and the temperature was maintained at 37 °C to eliminate changes in these variables and identify the effects of a change in [Ca^{2+}] only. We selected a citrate infusion of 1.5 ml kg^{-1} to obtain [Ca^{2+}] values encompassing the range of hypocalcaemia encountered clinically. The volume of either preservative added to blood during collection (ACD 15 ml *v.* CPD 14 ml solution per 100 ml whole blood) is approximate and the maximum difference in final citrate concentration in blood, after collection, is of the order of 5%. Therefore, we compared effects of ACD with those of CPD at equal rates of infusion.

Hedley-Whyte and associates (1976) noted the possible haemodynamic advantages of the i.v. infusion of CPD to the recipient of the blood. In our experiments, ACD and CPD infusion were followed by similar changes in [Ca^{2+}], and any haemodynamic advantages of one form of citrate over another were not observed. These findings are in good agreement with data of Olinger and colleagues (1976) who found that the haemodynamic consequences of ACD and CPD-stored blood were similar in patients following cardiac surgery and during haemodialysis.

Our data demonstrate that, in the intact normovolaemic dog, a transient decrease in [Ca^{2+}] is associated with a similar change in m.a.p. Up to 15 min following the infusion of ACD, a decrease in m.a.p. was recorded while CO was either increased (at the 5-min observation period) or not different from control. Thus the change in m.a.p. which occurred was secondary to a decrease in the resistance to flow in the peripheral vasculature. A change in ventricular function occurred also. If myocardial contractility remained unchanged, a decrease in m.a.p. (ventricular afterload) would be expected to be associated with increased CO without a change in or with a decrease of $\bar{P}_{PA_0}$. In our experiments, when m.a.p. decreased, CO was either increased (at the 5-min period) or not different from control and $\bar{P}_{PA_0}$ increased, thus suggesting left ventricular dysfunction in addition to the change in peripheral vascular function. The magnitude of alterations in the performance of the ventricular pump secondary to the decrease in $[Ca^{2+}]$ have been further defined recently in experiments in which data on the left ventricular function curve (LVFC) were collected during steady state deviations of $[Ca^{2+}]$ below normal while the major haemodynamic determinants of ventricular performance (m.a.p., HR) were controlled. LVFC were displaced markedly to the right and downward (Drop et al., 1978).

An effect of hypocalcaemia on the peripheral vasculature has received little attention in the past. It is possible that this peripheral site of action of hypocalcaemia has been overlooked or obscured in previous studies because of the nature of the experimental design, particularly with respect to the conditions present before the period of hypocalcaemia. For example, Bunker, Bendixen and Murphy (1962) may have overlooked the peripheral vascular manifestations of hypocalcaemia. These authors found that a decrease in the calculated $[Ca^{2+}]$ (range 0.16–0.54 mmol $litre^{-1}$) was associated with a decrease in m.a.p. and a variable change in CO. According to our evaluation of their results, total peripheral resistance decreased in four of five dogs. Cooper and associates (1973) evaluated ventricular responses to the transfusion of citrated blood in the dog following a 15-min period of arterial hypotension. This condition may have influenced baseline haemodynamic variables. Denlinger and Nahrwold (1976) described arterial hypotension in a patient following the rapid transfusion of citrated blood during blood loss associated with surgery. A decrease in arterial pressure was associated with an increase in central venous pressure. However, data on $\bar{P}_{PA_0}$ and CO were not presented and the status of the circulating blood volume was uncertain.

In clinical studies of the haemodynamic consequences of citrate-induced hypocalcaemia, the indices of haemodynamic function were recorded during and following the infusion of citrated whole blood administered to counteract a deficit in the circulating blood volume. Under these circumstances, the haemodynamic effects observed were not only those of hypocalcaemia but, in part also, those of volume loading. Hence, evaluation of the overall haemodynamic effects of hypocalcaemia may be less than satisfactory when performed in patients during blood transfusion. However, although it must be emphasized that the effects of citrate are of interest mainly in association with blood transfusion in the patient in whom the blood volume is likely to be reduced, it is important to determine the effects of a change in $[Ca^{2+}]$ alone. Therefore, in our experiments the haemodynamic consequences of the infusion of citrate were examined in the normovolaemic dog.

Our data are in agreement with those presented by Hinkle and Cooperman (1971) showing that the effects of the rapid infusion of citrated blood on $[Ca^{2+}]$ are transient in nature.

Our data are in contrast with those of Corbascio and Smith (1967) who investigated the effects of the infusion of citrate in dogs anaesthetized with nitrous oxide in oxygen with suxamethonium as the neuromuscular blocking agent. These authors showed that, following infusion of citrate, m.a.p. decreased in all animals and total peripheral resistance decreased in three of 11 dogs. A surprising finding in this study is that CO decreased without a change in peak left ventricular dP/dt. Unfortunately, $[Ca^{2+}]$ was not measured. Although the reason for this discrepancy in results is not clear, the large variation in the changes observed in the haemodynamic variables recorded by these authors may have been related to variations in depth of anaesthesia.

Controversy exists with respect to the need for calcium replacement therapy when decreased $[Ca^{2+}]$ occurs during the transfusion of citrated blood or haemodialysis. Although Miller (1973) and Howland and others (1977) have proposed that routine calcium replacement therapy in patients during and following blood transfusion is not required, the adjustment of $[Ca^{2+}]$ in patients may be appropriate when the disturbances in $[Ca^{2+}]$ are severe or exist for a prolonged period of time. The amount of calcium to be infused should be guided by measurements of $[Ca^{2+}]$. Clinically, calcium chloride 5 mg kg^{-1} may be administered and repeated if indicated by $[Ca^{2+}]$ measurement.

It appears that left ventricular dysfunction, noted in the presence of hypocalcaemia, was intensified by beta blockade. Before beta blockade, CO and SV were greater than control at the 5-min observation period. In contrast, small changes in these variables were insignificant at the same time interval following beta blockade, despite a similar increase in $P\overline{PA}_0$ and decrease in m.a.p. This finding may be important in patients presenting for major vascular or cardiac surgery. Propranolol therapy is common and transfusion of large amounts of banked blood is likely in these patients. It should be pointed out that conditions underlying the need for beta blocking drugs in patients may influence haemodynamic adjustment to citrate loading.

The intensification by beta blockade of hypocalcaemia-induced alterations in ventricular function may be explained on the basis of a severely impaired delivery of calcium to the contractile proteins. Two factors may be responsible. With the institution of low [Ca^{2+}] in the circulating blood, available calcium within the myocardial cell may be reduced. In addition, Naylor (1967) has proposed that propranolol may impede transport of calcium from the sarcoplasmic reticulum to the contractile elements. However, it is possible also that, during hypocalcaemia, myocardial function is supported by increased catecholamines. Beta blockade would antagonize the effects of these catecholamines.

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CONSEQUENCES HEMODYNAMIQUES DE L'INFUSION DE CITRATE SUR UN CHIEN ANESTHESIE: COMPARAISON ENTRE DEUX SOLUTIONS DE CITRATE ET INFLUENCE DU BLOCAGE BETA

RESUME

Nous avons comparé les effets d'une solution d'acide-citrate-dextrose (ACD) avec ceux d'une solution de citrate-phosphate-dextrose (CPD), infusées à un taux égal, sur la concentration d'ions du calcium du sang et sur les différents indices de performances hémodynamiques, sur 17 chiens. On a étudié l'influence du blocage adrénergique bêta sur ces variations. Les effets de l'ACD et du CPD ont été étudiés sur cinq chiens et les résultats ont été similaires. Les variations vasculaires périphériques ont constitué la principale cause de l'hypotension artérielle. Sur six chiens, le propranolol (à raison de 0,5 mg kg^{-1}) a intensifié le dérèglement du ventricule gauche, induit par l'hypocalcémie.

HÄMODYNAMISCHE FOLGEN EINER CITRATINFUSION IM NARKOTISIERTEN HUND; VERGLEICH ZWEIER CITRATLÖSUNGEN UND DIE EINWIRKUNG VON BETA-BLOCKADE

ZUSAMMENFASSUNG

Wir haben die Wirkungen einer Citratdextrosesäurelösung (ACD) mit denen einer, im gleichen Verhältnis eingeflossten Citratphosphatdextroselösung (CPD) auf die Blutkalziumkonzentration und verschiedene hämodynamische Leistungsindexe in 17 Hunden verglichen. Es wurde der Einfluss einer beta-adrenergischen Blockade auf diese Veranderungen untersucht. Die Wirkungen von ACD und CPD wurden in fünf Hunden studiert und erwiesen sich als gleichartig. Die Hauptursache fur arterielle Hypotonie waren periphere Gefässveränderungen. Bei sechs Hunden verstärkte 0,5 mg kg^{-1} Propanolol die durch Hypokalzämie herbeigeführte linksventrikulare Funktionsstorung.

CONSECUENCIAS HEMODINAMICAS DE LA INFUSION DE CITRATO EN EL PERRO ANESTESIADO: COMPARACION ENTRE LAS DOS SOLUCIONES DE CITRATO Y LA INFLUENCIA DEL BLOQUEO BETA

SUMARIO

Comparamos los efectos de una solución de dextrosa–citrato–ácido (DCA) con los de una solución de dextrosa–fosfato–citrato (DFC), infusadas al mismo ritmo, sobre la concentración del ión calcio en la sangre y sobre los distintos índices de performancia hemodinámica en 17 perros. Se examinó la influencia del bloqueo beta sobre dichas alteraciones. Se estudiaron los efectos de la DCA y de la DFC en cinco perros y éstos eran similares. Los cambios vasculares periféricos fueron la causa principal de la hipotensión arterial. En seis perros, el propanolol (0,5 mg kg^{-1}) intensificó la disfunción ventricular izquierda inducida por hipocalcemia.

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RESPONSE OF MEAN AND PHASIC CORONARY ARTERIAL BLOOD FLOW TO GRADED HYPERCAPNIA IN DOGS

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SUMMARY

An electromagnetic flow meter was used to assess the changes in coronary blood flow in response to four levels of increased Pa_{CO_2} in six dogs. Mean, diastolic and systolic flow all increased during hypercapnia, the increase being maximal at mean Pa_{CO_2} 11.3 kPa. Mean and diastolic coronary vascular resistances decreased progressively as Pa_{CO_2} increased, but systolic resistance, although decreasing with the lower levels of hypercapnia, returned to control at the greatest Pa_{CO_2}. Although the oxygen available to the myocardium was increased markedly during hypercapnia, coronary sinus Po_2 increased also, reflecting a reduction in myocardial oxygen extraction; thus myocardial oxygen consumption was unchanged. Cardiac output was increased significantly only at the greatest Pa_{CO_2}. Total body oxygen handling was not altered significantly.

A previous study (Ledingham et al., 1970) utilizing a radioactive inert-gas clearance technique to measure myocardial blood flow has shown that, in the intact anaesthetized dog, hypercapnia (Pa_{CO_2} 11.97–13.3 kPa) caused a considerable increase in the blood flow in the myocardium which was associated with an increase in the oxygen content of coronary sinus blood. No attempt was made to study in detail the effect on myocardial blood flow of increases in Pa_{CO_2} to tensions between 5.32 and 11.97 kPa. Therefore, the present study was undertaken to determine if these intermediate arterial carbon dioxide tensions were associated with corresponding changes in coronary blood flow and myocardial oxygen usage and to determine also if variation in the arterial carbon dioxide tension produced changes in the pattern of phasic coronary flow.

METHODS

Six healthy adult dogs of mixed breed (weight range 22–34 kg) were studied. Anaesthesia was induced with thiopentone 15–20 mg kg^{-1} and maintained with trichloroethylene 0.5–0.75% vaporized from a Tritec vaporizer (Cyprane Ltd). Suxamethonium chloride 50–100 mg was given i.v. or i.m. to facilitate tracheal intubation and thereafter i.m. as required to abolish reflex movements (usually every 45–60 min). Intermittent positive pressure ventilation of the lungs was provided by a Palmer sine-wave pump, the ventilation being adjusted to provide Pa_{CO_2}, for control measurements, of about 5.3 kPa. The ventilating gas consisted of a mixture of oxygen and nitrogen which was adjusted to produce Pa_{O_2} 12.6–14.0 kPa at all times. A copper–constantan thermocouple was sited in the oesophagus at cardiac level.

Under radiographic control, catheters were introduced into the thoracic descending aorta and the right atrium through the left femoral vessels and into the pulmonary artery and coronary sinus through the left internal jugular vein. A left thoracotomy was performed and, after incision of the pericardium, a short length (1–1.5 cm) of the circumflex or anterior descending branch of the left coronary artery was dissected free from the underlying myocardium. An electromagnetic flow transducer of luminal diameter 2.0 or 2.5 mm (Statham SP7515) was applied to the cleared segment of vessel so that a close fit was obtained. A larger flow transducer of luminal diameter 18 mm (Statham SP7516) was applied to the main trunk of the pulmonary artery after division of the ligamentum arteriosum and clearance of attached connective-tissue. The two flow transducers were connected to flow meters with non-occlusive zero facility (Statham SP2202). The lung was re-inflated and lung collapse minimized by the use of 5 cm H_2O positive end-expiratory pressure. Thus flow could be measured simultaneously in a major coronary vessel and in the pulmonary artery (cardiac output).

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Hypercapnia of a desired level was produced by adding the appropriate volume of carbon dioxide gas to the inspired gas mixture with a corresponding adjustment of oxygen flow to maintain a constant inspired oxygen concentration. The stability of $P\text{CO}_2$ was assessed by observing the expired carbon dioxide concentration using an infra-red carbon dioxide analyser (Hartman and Braun). Measurements were made and samples taken when all physiological variables had been stable for not less than 5 min. The mean time of exposure to carbon dioxide was 14 min. The effects of carbon dioxide were examined at the following tensions: approximately 7.3, 8.6, 9.9 and 11.3 kPa. Pa_{CO_2} was restored to control after each set of measurements at the increased Pa_{CO_2} and the order of producing the various levels of hypercapnia was randomized. In addition to the above, in five of the animals the effects of a greater Pa_{CO_2} (mean 14 kPa) were examined.

Blood-gas tensions and pH were measured using suitably calibrated electrodes (Instrumentation Laboratories, I.L. 182). Blood oxygen content was calculated from $P\text{O}_2$ allowing for "blood-gas factor" and any temperature difference between the electrode and the animal's mid-oesophagus. Haemoglobin was measured using a co-oximeter (Instrumentation Laboratories I.L. 213). Details of this calculation are included in a previous publication (Vance, Brown and Smith, 1973).

The following calculations were made also:

$$\underset{\text{(unit)}}{\text{Mean CVR}} = \frac{\text{Mean systolic art. pressure} - \text{RAP}}{\text{Mean CAF}} \times \frac{10}{1}$$

$$\underset{\text{(unit)}}{\text{Systolic CVR}} = \frac{\text{Systolic art. pressure} - \text{RAP}}{\text{Systolic CAF}} \times \frac{10}{1}$$

$$\underset{\text{(unit)}}{\text{Diastolic CVR}} = \frac{\text{Diastolic art. pressure} - \text{RAP}}{\text{Diastolic CAF}} \times \frac{10}{1}$$

$$\text{SVR (unit)} = \frac{\text{mean art. pressure} - \text{RAP}}{\text{CO}} \times \frac{10}{1}$$

$$\underset{(\text{ml min}^{-1})}{\text{Myocardial O}_2\text{ consumption}} = \frac{\text{mean CAF} \times (Ca_{\text{O}_2} - Ccs_{\text{O}_2})}{100}$$

$$\underset{(\text{ml min}^{-1})}{\text{Myocardial O}_2\text{ availability}} = \frac{\text{mean CAF} \times Ca_{\text{O}_2}}{100}$$

$$\underset{(\text{ml min}^{-1})}{\text{Total O}_2\text{ consumption}} = \text{CO} \times (Ca_{\text{O}_2} - C\bar{v}_{\text{O}_2}) \times 10$$

$$\underset{(\text{ml min}^{-1})}{\text{Total O}_2\text{ availability}} = \text{CO} \times Ca_{\text{O}_2} \times 100$$

$$\text{Myocardial O}_2\text{ extraction (\%)} = \frac{(Ca_{\text{O}_2} - Ccs_{\text{O}_2})}{Ca_{\text{O}_2}} \times \frac{100}{1}$$

where CAF = coronary artery flow; art. = arterial; CVR = coronary vascular resistance; SVR = systemic vascular resistance; RAP = right atrial pressure (mm Hg); CO = cardiac output (litre min^{-1}). Ccs_{O_2}, $C\bar{v}_{\text{O}_2}$, Ca_{O_2} = coronary sinus, mixed venous and arterial oxygen content (ml dl^{-1}).

In the above calculations, it was assumed that the coronary sinus blood was representative of the venous outflow of the region perfused by the artery of which the flow was being measured.

RESULTS

These are presented in tables which show, in four sets of columns, the control and test values (mean ± standard error of the mean) for each Pa_{CO_2}. Each set of values was compared with its own control using Student's t test for paired data. Table I shows that the graded increments in Pa_{CO_2} caused graded increases in coronary artery flow (CAF). The graded increases in mean CAF with Pa_{CO_2} increased to approximately 7.3, 8.6, 9.9 and 11.3 kPa were 19%, 35%, 53% and 84% respectively. The accompanying changes in arterial pressure were small, but significant decreases in heart rate occurred with the greater carbon dioxide tensions. In the five animals in which Pa_{CO_2} was increased beyond 11.97 kPa, the flow response was: Pa_{CO_2} 5.19 ± 0.133 kPa increased to 14.1 ± 0.532 kPa caused a mean increase in flow from 65 ± 8 ml min^{-1} to 119 ± 12 ml min^{-1}.

The per cent increases in systolic flow with increasing Pa_{CO_2} were 23%, 52%, 82% and 139% and the corresponding increases in diastolic flow were 7%, 24%, 46% and 62%; thus the relative systolic flow increases were greater than the diastolic. Figure 1 shows the per cent changes in mean, systolic and diastolic coronary vascular resistances. The changes in mean and diastolic resistance were parallel, whereas the systolic resistance showed a biphasic response, terminating at −1% at the greatest Pa_{CO_2}.

Arterial pH changes were appropriate for the carbon dioxide tensions attained and reflected an appropriate degree of respiratory acidosis (tables II and III). Similar changes occurred in coronary sinus and right atrial blood. The changes in coronary sinus

TABLE I. *Haemodynamic variables and vascular resistances associated with graded hypercapnia (mean* ± SEM). *CAF = coronary artery flow; CVR = coronary vascular resistance; SVR = systemic vascular resistance;* *$P < 0.05$

	Pa_{CO_2} (kPa)							
	5.45 ± 0.067	7.46 ± 0.172	5.19 ± 0.133	8.79 ± 0.133	5.19 ± 0.133	10.24 ± 0.133	5.32 ± 0.266	11.3 ± 0.133
Heart rate (beat min^{-1})	202 ± 10	202 ± 19	203 ± 14	* 178 ± 15	208 ± 18	* 172 ± 18	206 ± 8	* 172 ± 13
Mean arterial pressure (mm Hg)	130 ± 8	134 ± 8	135 ± 8	* 143 ± 9	133 ± 6	139 ± 6	131 ± 8	* 146 ± 5
Right atrial pressure (mm Hg)	0.5 ± 0.4	0.5 ± 0.3	0.8 ± 0.3	0.9 ± 0.4	0.5 ± 0.3	0.8 ± 0.5	0.4 ± 0.3	* 1.1 ± 0.3
Mean CAF (ml min^{-1})	62 ± 8	* 74 ± 10	60 ± 8	* 81 ± 10	64 ± 9	* 98 ± 15	64 ± 9	* 118 ± 14
Systolic CAF (ml min^{-1})	30 ± 7	* 37 ± 6	29 ± 5	* 44 ± 8	28 ± 6	* 51 ± 11	31 ± 6	* 74 ± 6
Diastolic CAF (ml min^{-1})	100 ± 13	107 ± 16	100 ± 11	* 124 ± 14	103 ± 13	* 150 ± 22	104 ± 14	* 169 ± 20
Cardiac output (litre min^{-1})	2.45 ± 0.31	2.77 ± 0.45	2.71 ± 0.23	3.39 ± 0.47	2.64 ± 0.3	3.0 ± 0.5	3.13 ± 0.4	* 3.62 ± 0.44
Mean CVR (unit)	22.3 ± 2.2	* 19.4 ± 2.2	23.9 ± 2.5	* 18.7 ± 2.0	22.0 ± 2.2	* 15.9 ± 2.7	21.9 ± 2.3	* 13.4 ± 1.7
Systolic CVR (unit)	50.6 ± 2.9	* 43.8 ± 3.2	54.1 ± 3.1	* 40.9 ± 2.8	41.0 ± 2.6	* 32.9 ± 3.4	49.3 ± 3.1	48.7 ± 3.7
Diastolic CVR (unit)	12.0 ± 1.1	11.5 ± 1.4	12.2 ± 1.3	10.3 ± 1.1	11.2 ± 1.5	* 8.1 ± 1.0	11.1 ± 1.3	* 7.5 ± 1.2
SVR (unit)	595 ± 90	573 ± 110	380 ± 90	390 ± 80	374 ± 92	426 ± 82	454 ± 60	459 ± 82

TABLE II. *Blood-gas tensions, pH and myocardial oxygen usage in response to graded hypercapnia (mean* ± SEM). *CS = coronary sinus; myocardial = that area of myocardium perfused by the coronary artery studied;* *$P < 0.05$

	Pa_{CO_2} (kPa)							
	5.45±0.067	7.46±0.172	5.19±0.133	8.79±0.133	5.19±0.133	10.24±0.133	5.32±0.266	11.3±0.133
Arterial pH (unit)	7.363±0.034	*7.282±0.039	7.412±0.021	*7.237±0.022	7.412±0.021	*7.178±0.028	7.375±0.028	*7.110±0.046
CS P_{O_2} (kPa)	3.72±0.266	*4.39±0.266	3.19±0.266	*4.92±0.399	3.19±0.399	*5.72±0.665	3.46±0.399	*6.78±0.798
Cc_{SO_2} (ml dl^{-1})	11±1.5	*13.1±0.9	8.8±1.0	*13.1±1.0	8.5±1.1	*14.2±2	9.1±1.5	*16.3±2.0
CS P_{CO_2} (kPa)	7.45±0.266	*8.91±0.186	7.58±0.133	*10.11±0.266	7.05±0.133	*11.97±0.532	7.18±0.133	*13.3±0.665
CS pH (unit)	7.322±0.027	*7.255±0.038	7.350±0.017	*7.197±0.023	7.342±0.012	*7.138±0.022	7.313±0.030	*7.078±0.039
Myocardial O_2 consumption (ml min^{-1})	8.9±1.4	9.5±1.1	9.5±0.9	9.0±0.9	10.6±1.3	10.5±1.5	9.8±1.1	10.2±2.1
Myocardial O_2 availability (ml min^{-1})	15.1±2.1	*18.0±2.5	15.0±1.8	*20.1±2.4	16.2±2.2	*25.1±2.7	15.8±1.8	*30.3±3.3
Myocardial O_2 extraction(%)	55±5	*46±3	65±5	*47±6	67±5	*44±8	65±6	*37±6

TABLE III. *Mixed venous blood-gas tensions, pH and total body oxygen usage in response to graded hypercapnia (mean* ± SEM). *$P < 0.05$

	Pa_{CO_2} (kPa)							
	5.45±0.067	7.46±0.172	5.19±0.133	8.79±0.133	5.19±0.133	10.24±0.133	5.32±0.266	11.3±0.133
Mixed venous P_{O_2} (kPa)	6.38±0.266	*7.32±0.133	5.85±0.532	*7.45±0.789	5.19±0.665	*7.18±0.798	5.85±0.798	*8.51±0.665
Mixed venous O_2 content (ml dl^{-1})	18.7±1.1	19.7±1.3	18.5±1.5	18.8±1.8	16.0±2.0	18.0±2.0	17.4±2.1	20.7±1.4
Mixed venous P_{CO_2} (kPa)	6.65±0.199	*8.11±0.213	6.52±0.532	*9.44±0.08	6.38±0.266	*11.17±0.266	6.25±0.133	*12.1±0.266
Mixed venous pH (unit)	7.353±0.039	*7.287±0.039	7.35±0.048	*7.263±0.025	7.365±0.018	*7.157±0.022	7.35±0.040	*7.11±0.043
Total O_2 consumption (ml min^{-1})	158±21	138±16	167±26	179±31	186±23	168±24	205±23	173±19
Total O_2 availability (ml min^{-1})	598±83	693±125	679±70	854±146	669±75	604±87	787±104	*947±131
Total O_2 extraction (%)	23±2	*19±2	28±8	27±9	33±9	30±10	29±9	29±12

$P\mathrm{O}_2$ showed a graded increase: 18%, 54%, 79% and 96%. These were reflected in increases in coronary sinus oxygen saturation and content.

The myocardium did not show significant alterations in oxygen consumption, although the oxygen availability was considerably increased at each carbon dioxide tension. There was a concomitant decrease in the oxygen extracted by the myocardium (table II). Total body oxygen handling did not exhibit consistent or significant changes (table III).

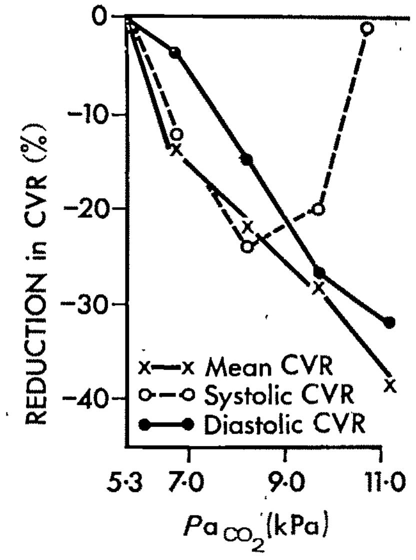

FIG. 1. Changes in mean, systolic and diastolic coronary vascular resistance (CVR) with graded hypercapnia.

DISCUSSION

The electromagnetic flow meter is a well-established method of measurement of vessel blood flow. It has several advantages over the radioactive inert-gas clearance methods used in previous investigations (Herd et al., 1962; Vance, Parratt and Ledingham, 1971). These include the ability to observe blood flow continuously and the ability to observe blood flow at different phases of the cardiac cycle.

The following disadvantages are associated with this method. The vessel under examination requires dissection and is, therefore, subject to surgical manipulation. The flow transducer should be fitted closely to the vessel and, as a result, the cross-sectional area of the vessel lumen may be reduced. This may impose a small increase in resistance to flow in the affected vessel, but this is likely to be negligible in relation to the total resistance of the vascular bed into which the vessel is flowing. It is not possible to measure tissue flow with the flow meter as may be done with the inert radioactive gas method.

Relative to human dose values, the doses of thiopentone used for the induction of anaesthesia in this study may seem large, but it is known that dogs require larger doses of barbiturates than do humans. Moreover, since the induction of anaesthesia with trichloroethylene is slow, a large dose of thiopentone was required to ensure that the animals would not recover consciousness before the trichloroethylene became effective.

The results of this study show that hypercapnia causes a decrease in coronary vascular resistance with an increase in blood flow. Therefore, they are in agreement with several previous publications (Feinberg, Gerola and Katz, 1960; Kittle, Aoki and Brown, 1965; Eberlein, 1966; Ledingham et al., 1970). In addition, this study illustrates that the extent of the increase in flow is related to $P\mathrm{a}_{\mathrm{CO}_2}$. Furthermore, it suggests that the maximal flow response occurred when $P\mathrm{a}_{\mathrm{CO}_2}$ was in the range 10.6–12.0 kPa, since the response of the animals when $P\mathrm{a}_{\mathrm{CO}_2}$ was increased to a greater value was identical to that when $P\mathrm{a}_{\mathrm{CO}_2}$ was 10.6–11.97 kPa. The changes in coronary vascular resistance were of interest. The mean and diastolic resistances decreased progressively. The response of the systolic resistance was different and showed an initial decrease followed by a return to control values. It would have been assumed that, with the decrease in heart rate which occurred with the higher values of $P\mathrm{a}_{\mathrm{CO}_2}$, the reduction in systolic time would have given rise to larger decrements in systolic resistance. However, there was an increase in right atrial pressure and, therefore, of ventricular filling pressure with $P\mathrm{a}_{\mathrm{CO}_2}$ increased to 10.6–11.97 kPa. Presumably this caused an increase in myocardial contractile force which would have imposed a greater extra-vascular resistance on the coronary vessels during systole. The other possible mechanism for an increase in myocardial contractile force during hypercapnia could be increased sympatho-adrenal activity.

The mechanisms of the vasodilator response to hypercapnia has not been examined here, but it has been shown that the response is unaffected by total adrenergic neurone blockade with bretylium and by beta-adrenoreceptor blockade with propranolol (Ledingham et al., 1970). Therefore, the response is not mediated through the sympathetic nervous system or by the release of catecholamines. It is not clear whether the flow changes observed are produced in response to carbon dioxide tensions or to the associated pH changes. Increases in myocardial blood flow have been recorded in response to metabolic acidosis induced artificially with lactic acid and with hydrochloric acid (Vance, 1974), although other workers have failed to demonstrate this effect with hydrochloric acid (Goodyer et al., 1961; Kittle, Aoki and Brown, 1965). Therefore the two have not been separated satisfactorily. Hypercapnia, with its associated acidosis, is a potent coronary vasodilator and has been shown to be as potent in this respect as severe hypoxaemia (arterial Po_2 2.66 kPa) (Vance, Parratt and Ledingham, 1971).

Since the arterial oxygen tension was maintained at a steady value of 12.6–14.6 kPa throughout the study, the arterial blood remained fully saturated. This, accompanied by the increase in coronary blood flow, resulted in large increases in the quantity of oxygen available to the myocardium. Since the oxygen consumption of the myocardium was unchanged, there was an increase in the oxygen contained in the coronary venous blood and a decrease in the extraction of oxygen by the myocardium—overperfusion relative to oxygen requirements.

It has been stated frequently that there is a close relationship between coronary flow and myocardial oxygen consumption (Braunwald et al., 1958; Feinberg, Katz and Boyd, 1962). This relationship is upset during hypercapnia, since myocardial oxygen consumption was unchanged while coronary flow increased.

Cardiac output increased at all values of Pa_{CO_2} but this was significant only at the greatest carbon dioxide tension. These slight increases in cardiac output accounted for the small increases in systemic arterial pressure since total vascular resistance remained unchanged.

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REACTION DU DEBIT SANGUIN CORONAIRE ARTERIEL MOYEN ET PHASIQUE A L'HYPERCAPNIE GRADUELLE CHEZ LES CHIENS

RESUME

On a utilisé un débitmètre électromagnétique pour évaluer les changements dans le débit sanguin coronaire, réagissant à quatre niveaux d'augmentation de la Pa_{CO_2} sur six chiens. Le débit systolique, a le débit diastolique et le débit moyen ont augmenté pendant l'hypercapnie, cette augmentation atteignant son point maximal à une Pa_{CO_2} moyenne de 11,3 kPa. Les résistances vasculaires coronaires moyenne et diastolique ont diminué progressivement au fur et à mesure qu'aumentait la Pa_{CO_2}, mais la résistance systolique, bien que diminuant avec les plus faibles niveaux d'hypercapnie, est retournée aux valeurs témoins au plus haut point de la Pa_{CO_2}. Bien que l'oxygène arrivant au myocarde ait augmenté d'une manière marquée pendant l'hypercapnie, le sinus coronaire Po_2 a aussi augmenté, ce qui reflète une réduction de l'extraction de l'oxygène du myocarde et la consommation d'oxygène du myocarde est donc demeurée inchangée. Le débit cardiaque n'a augmenté d'une manière significative qu'au point le plus élevé de la Pa_{CO_2}. La consommation totale d'oxygène du corps n'a pas été sensiblement modifiée.

REAKTIONEN DES MITTLEREN UND PHASISCHEN ARTERIELLEN KORONARBLUTFLUSSES AUF GRADUELLE HYPERKAPNIE BEI HUNDEN

ZUSAMMENFASSUNG

Ein elektromagnetisches Durchflussmessgerät wurde verwendet, um die Veränderungen des Koronar-Blutflusses als Reaktion auf vier Stufen von erhohtem Pa_{CO_2} bei sechs Hunden zu bewerten. Der mittlere diastolische und systolische stiegene alle während Hyperkapnie an, und der

maximale Anstieg ergab sich bei mittlerem Pa_{CO_2} 11,3 kPa. Der mittlere und diastolische Gefässwiderstand fiel progressiv mit steigendem Pa_{CO_2} während der systolische Widerstand zwar mit den niedrigener Stufen der Hyperkapnie fiel, aber beim hochsten Stand von Pa_{CO_2} zum Kontrollwert zurückkehrte. Obwohl der dem Myokardium verfügbare Sauerstoff wahrend der Hyperkapnie deutlich anstieg, stieg auch der Koronar-Sinus Po_2, was eine Reduktion der myokardialen Sauerstoffextraktion anzeigt, weshalb der myokardiale Sauerstoffverbrauch unverändert blieb. Das Herzminutenvolumen stieg deutlich nur beim grössten Wert von Pa_{CO_2}. Der gesamte Sauerstoffkreislauf des Körpers zeigte sich nicht wesentlich verändert.

RESPUESTA DEL FLUJO SANGUINEO ARTERIAL CORONARIO FASICO Y MEDIO A LA HIPERCAPNIA GRADUADA EN PERROS

SUMARIO

Se usó un medidor de flujo electromagnético para evaluar en seis perros las alteraciones del flujo sanguíneo coronario en respuesta a cuatro niveles de Pa_{CO_2}. Durante la hipercapnia, aumentaron todos los flujos, el sistólico, el diastólico y el medio, siendo el incremento maximal (11.3 kPa) cuando el Pa_{CO_2} alcanzaba la media. Las resistencias vascular coronaria diastólica y media disminuyeron progresivamente a medida que aumentaba el Pa_{CO_2}, pero la resistencia sistólica, no obstante su descenso en los niveles inferiores de hipercapnia, volvió al control cuando el Pa_{CO_2} llegó a su máximo. Aunque el oxígeno disponible para el miocardio aumentara notablemente durante la hipercapnia, el seno coronario Po_2 también subió, reflejando una reducción de la extracción miocardial de oxígeno y, por ende, no se alteró el consumo miocardial de oxígeno. La función cardíaca aumentó significativamente sólo cuando el Pa_{CO_2} se hallaba en el máximo. No se modificó de manera significativa el manipuleo del oxígeno del cuerpo en total.

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EXPERIENCE WITH SPINAL ANALGESIA IN A BRITISH OBSTETRIC UNIT

J. S. CRAWFORD

SUMMARY

A series of 443 spinal anaesthetics is described. The procedures included operative vaginal delivery, removal of retained placenta and a miscellaneous group common to most obstetric units. Failure to provide effective relief of pain occurred in 5.2% of patients. There was one potentially serious complication, but with this exception hypotension was not a feature. Headache following spinal analgesia was experienced by 16.3% of patients, the frequency being greater among those who received spinal analgesia at or shortly after delivery, but was unrelated to the size of the needle (23-gauge or 25-gauge) used. Extradural blood patch promptly and permanently cured the headache. The duration of sensory and motor loss after operation varied considerably with the local anaesthetic agent used. The re-introduction of spinal analgesia into British obstetric anaesthetic practice is advocated.

Spinal block analgesia has suffered what many now consider to have been an unwarranted opprobrium in the United Kingdom during the past 30 yr. This has been so despite the fact that in North America, where the standards of anaesthetic care and the reporting of misadventures are at least the equal of ours, the method has been extensively used throughout that period. There are many advantages to the use of spinal analgesia, and it is disappointing that the majority of anaesthetists in training during the past 2–3 decades have received little or no guidance on the administration of a spinal block, because of the prejudice or, more commonly, the inexperience of their consultants.

The increasing interest in the application of regional analgesia in obstetric anaesthetic practice gives promise that experience gained in this subdivision of anaesthetic practice will herald the spread of the popularity of spinal analgesia to other provinces of anaesthesia. Our own experience with the technique, whilst infinitesimal in comparison with that of centres in the United States and Canada, is now considerable. We report it in the hope that others will be encouraged thereby to employ it more frequently.

MATERIALS AND METHOD

The technique of administration was standard and has been described in detail elsewhere (Crawford, 1978). Three drugs have been used. Initially we injected cinchocaine (2.5 mg of the drug in 1.0 ml of 5% dextrose), but when this became unavailable for some time as a result of manufacturing difficulties, we elected to use 5.0% lignocaine in 7.5% dextrose, a solution produced as a routine for many years, by the Department of Pharmacy in the Queen Elizabeth Medical Centre. Heavy Citanest (5% prilocaine in 6% dextrose), which appeared on the market rather briefly some time ago, has been used also. The volume administered was approximately 1.25–1.50 ml irrespective of the identity of the agent. We have relied upon manipulation of maternal posture to induce the required extent of sensory blockade. When a sacral block only was required (as for re-suture of the perineal wound) the patient remained in the erect sitting position for at least 15 s after completion of the injection. If a sensory block extending to T10 was needed (as for a mid-cavity forceps delivery, or removal of a retained placenta), the mother was returned promptly to the supine tilted position (on a wedge) after having sat erect for 5 s following completion of the injection.

Two sizes of spinal needle have been used. Originally we used a 23-gauge non-disposable needle without an introducer. More recently, in the expectation of reducing the frequency of post-spinal headache, we have used a 25-gauge disposable needle (Steriseal) with the aid of a 3.5-in. (8.75-cm) 20-gauge introducer advanced into the ligamentum flavum. Little or no attempt has been made to regulate the direction of the level of the needle in relationship to maternal tissues. The solution was injected at a

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steady rate throughout a period of approximately 10 s.

Selection of patients

In the context of a very intensive "extradural service" the number of prospective candidates has been small. The indications for spinal analgesia have been:

delivery by forceps, or breech, or of a multiple pregnancy, of a patient who had not received an extradural block;

removal of a retained placenta in a patient who had no extradural block;

evacuation of retained products of conception (excluding patients admitted for termination of pregnancy, who are likely to have an extradural block); in this category we have tended not to include patients who have recently aborted spontaneously, as they are understandably upset and would, we believe, prefer to be asleep during the operation;

primary repair of an extensive perineal tear, or re-suture of an episiotomy;

insertion of a Shirodkar suture (as an alternative to an extradural block);

miscellaneous surgical procedures on the perineum or cervix.

The assessment of the success or otherwise of the procedure has been based upon the evaluation reported by the patient during the routine interview on the following day. At the same time the patient was asked to estimate, to the nearest hour, the duration of sensory and motor loss. Direct enquiry was made as to whether or not the patient had a headache, and this enquiry was repeated daily on each of the following 5 days, or for as long as the patient remained in hospital.

RESULTS

Spinal analgesia was given for the vaginal delivery of 233 patients (nine breech, two multiple pregnancy, one spontaneous delivery and the remainder forceps). A 23-gauge needle was used in 160 of these patients. Manual removal of a retained placenta was conducted specifically under spinal analgesia in 65 patients; a 23-gauge needle was used in 40 of these. The number of "miscellaneous" patients totalled 145 (a 23-gauge needle was used in 91 of these), predominantly re-suture of perineum and evacuation of retained products of conception, but four patients who had a Shirodkar suture inserted and one who underwent haemorrhoidectomy post-natally were included.

Out of the total of 443 patients there was failure to initiate analgesia on five occasions (1.1%)—once in the vaginal delivery series and twice each in the other two groups. As a result, a general anaesthetic was given to each of these patients. The spinal block failed to provide complete relief in a further 18 patients (4.1%); seven patients undergoing forceps delivery, none of whom received a general anaesthetic; six patients undergoing removal of retained placenta, of whom five were consequently given a general anaesthetic; and five other patients, of whom three received a general anaesthetic.

The reported duration of motor and sensory block varied markedly with the local anaesthetic used, but not with the character of the obstetric or surgical procedure performed. The mean duration of sensory block among patients from whom an estimate was obtained was: cinchocaine (68 patients) 8.8 h, prilocaine (21 patients) 5.1 h, lignocaine (271 patients) 2.9 h. Respective mean duration of motor loss were: cinchocaine 7.0 h, prilocaine 4.5 h, lignocaine 2.8 h.

There was one major complication. A patient's membranes ruptured spontaneously at 23 weeks' gestation. She was kept in hospital and given uterine depressants, but 3 weeks later the umbilical cord prolapsed through a cervix which was only partially dilated. Spinal analgesia was administered as a matter of urgency as she was in pain and it was thought that she would be delivered rapidly. Inadvertently, a rather larger dose of lignocaine (2 ml) was injected, and because of maternal distress and some degree of unco-operation, it is doubtful that she sat upright for more than 2–3 s after completion of the injection. The block extended cephalad at a moderate pace and the patient began to complain of difficulty in breathing some 15 min after the injection. An endotracheal tube was passed with ease, as a precautionary measure. Peak spread of the sensory block (to T2) was reached 20 min after the injection. At no time was it necessary to assist ventilation. The endotracheal tube was removed about 30 min after intubation. The arterial pressure had decreased from a pre-spinal value of 115/70 mm Hg to 65/30 mm Hg by the time respiratory embarrassment became a feature. The hypotension was promptly and effectively reversed by the i.v. injection of ephedrine 10 mg accompanied and followed by the rapid infusion of 1.5 litre lactated Ringer's solution. The block had been administered at 20.00 h and by midnight the sensory block had worn off and the labour became painful. A lumbar extradural block was therefore provided at 00.10 h and the patient delivered at 04.50 h. The only noteworthy sequel was a post-spinal headache which was relieved by an extradural blood patch.

Apart from this event, headache was the only noteworthy complication associated with the spinal technique. The frequency of headache following spinal analgesia (table I) appeared to have been influenced little by the choice of spinal needle, and was least among those patients whose pregnancy had ended (as either an abortion or a term-delivery) some days before the procedure.

TABLE I. *Percentage frequency of typical post-spinal headache among groups of patients categorized according to the calibre of spinal needle used and to the operative procedure. The numbers in brackets are the total number of patients in each category*

	23-Gauge	25-Gauge
Vaginal delivery	17.5 (160)	15.1 (73)
Retained placenta	22.5 (40)	20.0 (25)
Other	12.1 (91)	14.8 (54)

The provision of an extradural blood patch was introduced into our unit some considerable time after the start of the series under review. It is our current practice to offer a blood patch to those of our patients who experience a headache after spinal analgesia, and 29 of these patients accepted the offer, received the patch and were immediately relieved of the headache without further complication.

A significant decrease in arterial pressure did not occur in any patient other than the one described in detail above.

One further observation is worthy of report. A patient, having aborted spontaneously, received a spinal block for the evacuation of the retained products of conception. In a previous pregnancy she had been delivered by Caesarean section. The only discomfort felt by the patient during the uterine evacuation was pain at the site of the Caesarean section scar; possibly an instance of a "spinal sieve" analagous to the "epidural sieve" (Crawford, 1976).

DISCUSSION

The total success rate of this procedure in our hands has been reasonably high (94.8%). There have been two main causes of failure. Failure to initiate spinal analgesia was a result, in possibly three of the five occasions recorded, of misunderstanding. It is not always possible to aspirate cerebrospinal fluid through a very narrow-gauge spinal needle which has penetrated the dura, and successful entry might not be appreciated, leading to abandonment of the procedure. Subsequent development of a typical post-spinal headache serves to demonstrate the fallacy. Insufficient analgesia results usually from the failure to achieve a block which extends to T10 in patients who require a low or mid-cavity forceps delivery or the manual removal of a retained placenta. The frequency of this category of failure has diminished year by year in our hospital.

The duration of sensory and motor block after operation varied in the expected manner with the identity of the local anaesthetic. In the context of obstetric practice, as conducted in this country, there seems little justification for not choosing to use lignocaine. Chloroprocaine might offer a better alternative were it to become available in the appropriate formulation. We appreciate that the lignocaine solution provided for us by our Pharmacy Department has not met with official approval by the national bodies concerned with pharmaceuticals, and that clinicians will, for the time being at least, have to continue to rely upon their local pharmacists for supplies.

The frequency of post-spinal headache in this series is disappointingly high. There is no doubt that the headaches did occur and were of the classic postural type. They commenced on the first, occasionally the second, day after operation, and among those patients who did not receive an extradural blood patch the headache invariably persisted for 5–6 days. After some experience we could, with confidence, promise the affected patient that the headache would clear on the 6th day, and the promise was never broken. The frequency is greatly in excess of that which is quoted authoritatively. Phillips and colleagues (1969), using predominantly a 25- or 26-gauge needle in their series of 10 440 patients, found a frequency of 3.5% post-spinal headache, a figure which accords well with most of those quoted by Bonica (1967) in his review of the relevant literature. There are two factors which might have contributed to the high frequency which we have encountered. Possibly the pregnant patient differs, as in so many other particulars, from the non-pregnant in the propensity with which a headache results from dural puncture (Bonica, 1967). It might be of some significance in this regard that 17.8% of the 298 "peri-delivery patients" (vaginal delivery or retained placenta) experienced a spinal headache whereas, of the 145 patients whose spinal analgesia was administered in the context of obstetric care but usually some time after pregnancy had ended, the frequency was 13.1%. The second factor is that we made no effort to ensure that our patients remained bed-fast (still less that they remained horizontal) for any appreciable length of time after the procedure. To have done so would have been to run counter to our hospital policy of encouraging close maternal–infant relationship at the earliest reasonable time after delivery.

The introduction of the technique of extradural blood patch, and our increasing confidence in the safety, as well as in the effectiveness of this therapy, has reduced our anxiety about the prospect of headache.

The one potentially serious complication encountered in this series served mainly to demonstrate that, even in the event that a high spinal block is produced inadvertently, the rate of deterioration in the patient's condition is such that it is inconceivable that any serious harm should result if a competent medical attendant, and the appropriate elementary implements of resuscitation, are available immediately. If either of these conditions cannot be met, that is, if there can be no guarantee of a doctor competent and equipped to perform endotracheal intubation and to apply intermittent positive pressure ventilation with an adequacy of oxygen through an endotracheal tube, then the use of spinal analgesia should be avoided except as a life-saving measure for mother or infant.

Hypovolaemia should be considered a contra-indication to spinal analgesia. In the rare circumstance that considerable haemorrhage has attended the complete or partial retention of a placenta, or that blood loss from a vulvo–vaginal wound has been excessive, appropriate replenishment of circulating blood volume should be completed before initiation of spinal analgesia. If haemorrhage of such proportion occurs during the course of the obstetric procedure, subsequent to the establishment of the spinal analgesia, management is no different from that which would be applicable were the patient to have received extradural analgesia.

CONCLUSIONS

We believe that our experience justifies our plea that spinal analgesia be re-introduced on a considerable scale to British obstetric anaesthetic practice. We do not advocate its general use for Caesarean section, for reasons detailed elsewhere (Crawford, 1978) but, for the categories of procedure referred to in this report, we believe it to offer outstanding advantages. In obstetric units which encompass an "extradural service" the place of spinal analgesia will be limited, but as is evident from this account, even in our own hospital, in which 70% of patients in labour receive an extradural block, spinal analgesia is provided quite frequently. In obstetric units which cannot offer a liberal extradural service, the facility to provide spinal analgesia for operative vaginal delivery, the removal of retained placenta, postpartum exploration of the uterus, post-partum perineal surgery, insertion of Shirodkar suture, and the like, must surely be accepted as being outstandingly preferable to reliance upon general anaesthesia (with its attendant dangers, unpleasantness and elimination of prompt maternal–infant rapport) or upon the relative ineffectiveness of pudendal block. The immediate complications of spinal analgesia used in the manner described, in a well-ordered and informed obstetric unit, will be of a very low order indeed provided that the simple guidelines respecting hypovolaemia and the availability of skilled aid are adhered to. The author's personal view is that there is no objection to spinal analgesia being administered, in the manner described, by obstetricians, provided that the latter have been trained under anaesthetic supervision and are able to provide elementary resuscitation, and that there is assurance that anaesthetic aid will be forthcoming promptly if required.

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EXPERIENCE AVEC L'ANALGESIE RACHIDIENNE DANS UNE CLINIQUE BRITANNIQUE D'OBSTETRIQUE

RESUME

On décrit dans cet article une série de 443 anesthésies rachidiennes. Parmi les interventions effectuées, il y a eu des accouchements opératoires par le vagin, des extractions de

placenta non évacué, et un groupe de divers commun à la plupart des cliniques d'obstétrique. On a constaté un échec dans le soulagement efficace de la douleur dans 5,2% des cas. Il y a eu une complication qui aurait pu être grave, mais à cette exception près, l'hypotension n'a pas été caractéristique. Des maux de tête après l'administration d'un analgésique rachidien ont été constatés dans 16,3% des cas, la fréquence étant plus grande parmi les femmes qui avaient reçu un analgésique rachidien au moment de l'accouchement ou juste après, ceci n'ayant toutefois aucune relation avec la dimension de l'aiguille utilisée (calibre 23 ou 25). L'obturation extradurale a éliminé rapidement et d'une manière permanente ces maux de tête. La durée de la perte de la faculté sensorielle et motrice après l'opération a varié d'une manière considérable suivant l'agent anesthésiant utilisé. On recommande dans cet article la réintroduction de l'analgésie rachidienne dans la pratique d'anesthésie britannique en matière d'obstétrique.

ERFAHRUNGEN MIT RÜCKENMARKS-ANALGESIE IN EINER BRITISCHEN GEBURTENKLINIK

ZUSAMMENFASSUNG

Beschrieben wird eine Serie von 443 Rückenmarks-Anästhesien. Zu dem Verfahren gehorten eine operative vaginale Geburt, Entfernung der Placenta und eine gemischte Gruppe, wie sie meist in Geburtshilfe-Einheiten vorkommt. Bei 5,2% der Patientinnen konnte keine wirksame Schmerzlinderung erzielt werden. Es gab eine potentiell ernsthafte Komplikation, aber von dieser Ausnahme abgesehen war Hypotension kein Problem. Kam es 16,3% der Patientinnen nach der Spinal-Analgesie zu spinalen Kopfschmerzen—mit grosserer Häufigkeit bei Patientinnen, die Spinal-Analgesie bei oder kurz nach der Geburt erhalten hatten, doch ohne Bezug auf die Grösse der dabei verwendeten Nadel. Ein extraduraler Bluteinreibuns-fleck beseitigte den Kopfschmerz rasch und permanent. Die Dauer des Empfindlichkeits- und Beweglichkeitsverlustes nach der Operation variierte mit der Art des verwendeten Lokalanästhesiemittels. Die Wiedereinführung von Spinal-Analgesie in die Narkosepraxis britischer Geburtshilfe wird empfohlen.

EXPERIMENTOS MEDIANTE ANALGESIA ESPINAL EN UNA UNIDAD OBSTETRICA BRITANICA

SUMARIO

Se da una descripción de una serie de 443 anestesias espinales. Las intervenciones incluían parto vaginal quirúrgico, remoción de placenta retenida, y un grupo mixto común a la mayoría de las unidades obstétricas. En un 5,2% de los pacientes, no fue posible aliviar el dolor de manera eficaz. Hubo una complicación potencialmente grave, pero, con esta excepción, la hipotensión no constituyó una característica. En un 16,3%, los pacientes sufrieron de dolor de cabeza postespinal después de la analgesia espinal, siendo más frecuente éste entre las personas que recibieron analgesia espinal en el momento del parto o poco después, pero esto no tenína relación alguna con el tamaño de la aguja (calibre 23 ó 25). La placa de sangre extradural curó el dolor de cabeza rápida y permanentemente. La pérdida sensorial y motora después de la operación varió considerablemente en función del agente anestético local utilizado. Se recomienda la reintroducción de la analgesia espinal en la aplicación de anestesia en la obstetrica británica.

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DIAZEPAM AND DROPERIDOL AS I.V. PREMEDICANTS

G. P. HERR, J. T. CONNER, R. L. KATZ, F. DOREY, J. L'ARMAND AND D. SCHEHL

SUMMARY

The effects of i.v. diazepam and droperidol both alone and in combination administered as premedication were studied in 240 patients. Relief of anxiety, sedation, lack of recall, acceptance by both patient and physician and side-effects were evaluated. Overall, the combination of droperidol 2.5 mg with diazepam 5 mg produced better ratings of these variables than could be achieved with either droperidol 10 mg or diazepam 10 mg alone. Larger doses of droperidol with diazepam produce an increased frequency of anxiety; larger doses of diazepam with droperidol may cause over-sedation.

In a previous study (Conner et al., 1978) fentanyl and morphine were studied both alone and and in combination with droperidol. The results were largely unfavourable to droperidol because of poor acceptance by the patient. We have studied droperidol alone at a greater dose and in combination with diazepam, hoping to improve acceptance by the patient. Relief of anxiety, sedation, lack of recall, acceptance by both patient and physician and side-effects were evaluated.

METHODS

Two hundred and forty patients (ages 18–69 yr, mean 38.7 yr) in good health and undergoing a variety of operative procedures with the exception of cardiac surgery and neurosurgery were studied. None had received a sedative or narcotic on the day of study.

One hour before surgery an i.v. infusion was started and the drugs were administered i.v. over a 1-min period. When in combination with droperidol, diazepam was given first. The drugs were administered in a double-blind manner using a randomized Latin-square sequence: droperidol 5 mg and 10 mg, diazepam 5 mg and 10 mg, and the combinations diazepam 5 mg plus droperidol 2.5 mg, diazepam 10 mg plus droperidol 2.5 mg, diazepam 5 mg plus droperidol 5 mg and diazepam 10 mg plus droperidol 5 mg. Each group consisted of 30 patients.

All observations before operation were made by a trained nurse observer. Before premedication, the patient was asked to evaluate his level of anxiety as negligible, mild, moderate or severe. Four minutes after the injection of the drug his sedation as compared with the unpremedicated state was rated as 0 (unchanged), 1+, 2+, 3+, 4+ (improved), or 1−, 2−, 3−, 4− (worsened). The patient was asked to rate the level of anxiety in comparison with the unpremedicated state using a similar scale. The evaluation of sedation and the relief of anxiety was repeated at 8, 16 and 32 min. Any signs of drug sensitivity or side-effects were noted.

The patients were shown a randomized series of "memory cards" (pictures of familiar objects or scenes) at 1, 2, 4, 8, 16 and 32 min to allow testing of recall.

The anaesthetists rated the premedication without knowledge of the nature of medication. The overall effect was graded poor (0), fair (1+), good (2+) or excellent (3+). They stated whether they would like their patients to receive the medication again. Comments on what they liked or disliked most about the effect of the drug were invited.

Interviews at 24 h after operation were made by the nurse observer who was unaware of the identity of the premedicant. The patients were asked to rate the study drugs as poor (0), fair (1+), good (2+) or excellent (3+) and if they would like to have the drug again.

Each patient was asked to identify the "memory cards" from a composite picture of eight pictures. Evidence of recall for the administration of the drug, the operating room and the recovery room was sought. Statistical analysis of the evaluations by both patient and nurse were carried out by transforming the raw scores to ridits based on the corresponding diazepam scores at 4 min. Ridit scores for the degree of acceptance by the patient and physician were based also on the corresponding diazepam scores.

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Overall differences between group means were tested with a Chi square statistic. Paired comparisons were tested by a Bonferroni procedure using an appropriate Z statistic. Significance was taken at the 5% level. This is a conservative statistical approach to the analysis of the data.

RESULTS

No statistically significant correlation could be demonstrated between the height, weight or age of the patient and the variables studied.

Anxiety (*table I and fig.* 1 (*Ridit score*))

Diazepam 10 mg produced significantly better relief of anxiety than diazepam 5 mg at all times. While droperidol 10 mg provided slightly greater scores for relief of anxiety over droperidol 5 mg, the difference was not significant. At 4 min, diazepam was better than droperidol while at 32 min the response to droperidol was better than that to diazepam.

In all patients, the addition of droperidol to diazepam produced a significant improvement over either droperidol or diazepam alone. No significant dose effect was demonstrated, thus the responses to diazepam 5 mg and diazepam 10 mg in combination with droperidol at either the 2.5 mg or 5 mg dose were similar.

Sedation (*table I and fig.* 2 (*Ridit score*))

The curves are statistically indistinguishable from those of the relief of anxiety as scored by the patient.

TABLE I. *Anxiety and sedation* (*mean scores*). *DZ = diazepam*; *DR = droperidol*

	Diazepam 5 mg	Diazepam 10 mg	Droperidol 5 mg	Droperidol 10 mg	DZ 5 mg + DR 2.5 mg	DZ 10 mg + DR 2.5 mg	DZ 5 mg + DR 5.0 mg	DZ 10 mg + DR 5.0 mg
By patient								
(0 ± 4)								
4 min	1.02	2.02	0.28	1.05	1.52	2.05	1.58	2.40
8 min	0.95	2.02	0.82	1.38	2.45	3.27	2.95	3.50
16 min	0.67	2.20	1.55	2.17	3.27	3.90	3.60	3.87
32 min	0.55	1.90	2.05	2.75	3.52	4.00	3.81	3.95
By nurse observer								
(0 ± 4)								
4 min	0.50	1.68	0.17	0.08	1.13	1.65	1.36	3.27
8 min	0.20	1.72	0.22	1.23	2.48	3.17	2.63	3.33
16 min	0.10	1.48	1.17	1.83	3.57	3.87	3.45	3.89
32 min	0.19	1.43	1.74	2.50	3.43	4.00	3.79	3.95

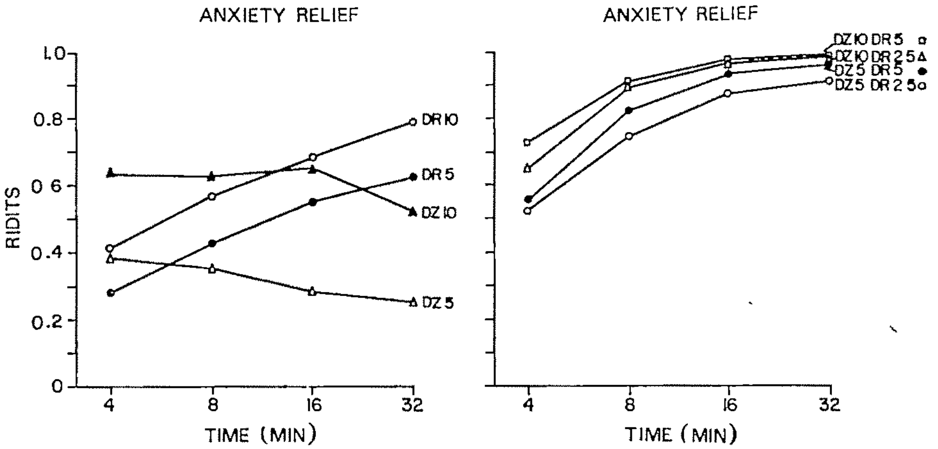

FIG. 1. Mean change in anxiety scored by the patient compared with the patient's unpremedicated state *v*. time from injection. DZ = diazepam, DR = droperidol; dose in mg. The higher the score the greater the relief of anxiety.

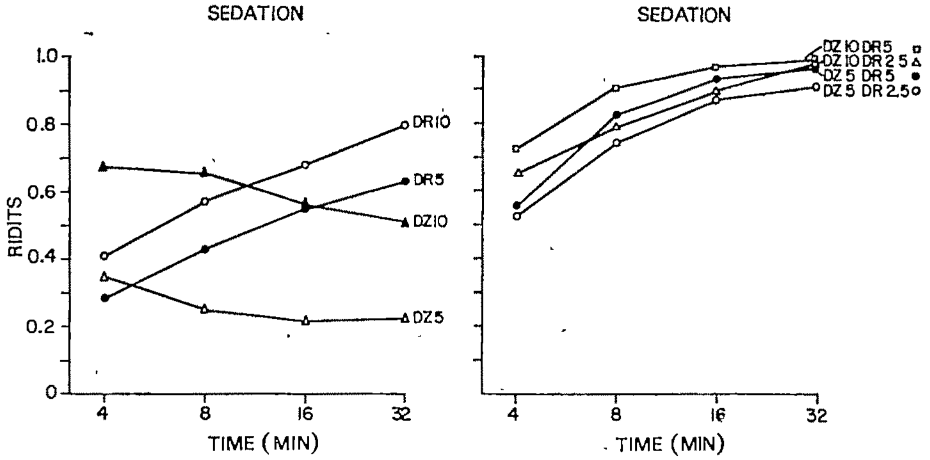

FIG. 2. Mean change in sedation scored by the observer compared with the patient's unpremedicated state *v.* time from injection. DZ = diazepam, DR = droperidol; dose in mg. The higher the score the greater the sedation.

TABLE II. *Patient acceptance at 24 h. Percentage of patients scoring* 0 (*poor*), 1 (*fair*), 2 (*good*) *or* 3 (*excellent*); *mean and ridit scores; percentage of patients who would take drug again* (*repeat*). *DZ = diazepam; DR = droperidol*

	Diazepam 5 mg	Diazepam 10 mg	Droperidol 5 mg	Droperidol 10 mg	DZ 5 mg + DR 2.5 mg	DZ 10 mg + DR 2.5 mg	DZ 5 mg + DR 5.0 mg	DZ 10 mg + DR 5.0 mg
Poor	30	7	31	10	14	3	10	7
Fair	27	7	28	23	11	7	23	0
Good	40	53	31	37	32	31	37	23
Excellent	3	33	10	30	43	59	30	70
Mean score	1.17	2.13	1.21	1.67	2.04	2.45	1.87	2.57
Ridit score	0.362	0.637	0.377	0.503	0.618	0.735	0.557	0.778
Repeat (%)	57	90	50	53	82	89	73	90

Acceptance by the patient 24 h after surgery (*table II and fig.* 3 (*Ridit score*))

The acceptance of diazepam 10 mg was significantly better than either diazepam 5 mg or droperidol 5 mg. Droperidol 10 mg was significantly better than diazepam 5 mg. The combination of droperidol 2.5 mg and diazepam 5 mg was significantly better than diazepam 5 mg or droperidol 5 mg alone, but not significantly better than droperidol 10 mg or diazepam 10 mg. While greater doses of diazepam and droperidol in combination scored higher than droperidol 2.5 mg with diazepam 5 mg, the difference was not significant.

Acceptance by the physician (*table III and fig.* 3 (*Ridit score*))

No significant dose effect was demonstrated for either drug or combination. Droperidol in all doses both alone and in combination was scored significantly higher by physicians than diazepam at either 5 mg or 10 mg.

Failure to recall

Recall data were expressed as per cent failing to recall the given memory card (maximum 17% at 1 min). Diazepam 5 mg had little effect on recall. There was a slight effect with droperidol 5 mg (maximum 24–26% at 16–32 min). Diazepam 10 mg had a maximum effect of 53% at 1–2 min following injection and decreasing to 35% by 32 min. Droperidol 10 mg alone had essentially no effect until 32 min, when it was similar to diazepam during the 1st min (52%). The combinations containing diazepam 5 mg had greater than 40% effect from 8 to 32 min. The combinations with diazepam 10 mg had greater than 40% effect from 1 to 32 min from injection and

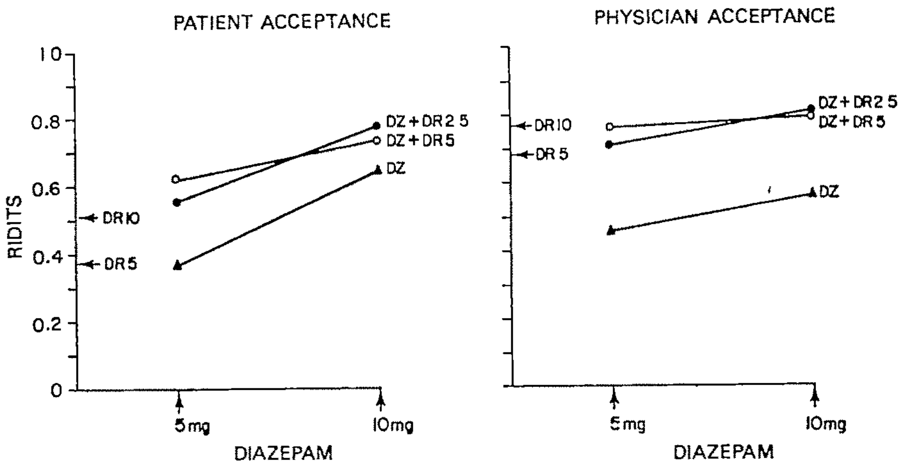

FIG. 3. Mean patient acceptance as scored by the patient 24 h after surgery and the mean physician score *v.* the dose of diazepam (DZ) for diazepam alone and in combination with droperidol (DR). The acceptance by patient and physician for droperidol alone is marked. Dose in mg. The higher the score the greater the degree of acceptance.

TABLE III. *Physician's acceptance at surgery. Percentage of patients scoring* 0 (*poor*), 1 (*fair*), 2 (*good*) *or* 3 (*excellent*); *mean scores; percentage of physicians who would use the drug again* (*repeat*). *DZ = diazepam; DR = droperidol*

	Diazepam 5 mg	Diazepam 10 mg	Droperidol 5 mg	Droperidol 10 mg	DZ 5 mg + DR 2.5 mg	DZ 10 mg + DR 2.5 mg	DZ 5 mg + DR 5.0 mg	DZ 10 mg + DR 5.0 mg
Poor	55	43	25	14	10	10	21	10
Fair	34	36	25	24	37	30	28	20
Good	11	18	39	52	43	40	41	60
Excellent	0	3	11	10	10	20	10	10
Mean scores	0.552	0.821	1.36	1.59	1.53	1.70	1.41	1.70
Repeat (%)	44	48	54	57	80	59	66	77

TABLE IV. *Side effects* (%) *before operation. DZ = diazepam; DR = droperidol*

	Diazepam 5 mg	Diazepam 10 mg	Droperidol 5 mg	Droperidol 10 mg	DZ 5 mg + DR 2.5 mg	DZ 10 mg + DR 2.5 mg	DZ 5 mg + DR 5 mg	DZ 10 mg + DR 5 mg
None	70	37	61	60	67	57	37	60
Dizziness	27	40	4	7	23	33	30	20
Increased anxiety	3	0	21	23	10	3	7	7
Crying	0	0	11	3	0	3	3	3
Restlessness	0	0	14	17	7	3	10	3

appeared to plateau at 4–8 min. Maximums: diazepam 5 mg plus droperidol 5 mg 77%, diazepam 10 mg and droperidol 2.5 mg 83%.

None of the drugs produced much effect on lack of recall of the operating room. Lack of recall in the recovery period did not appear to be related to the premedication.

Side-effects in more than 10% *of patients* (*table IV*)

Diazepam caused dizziness initially in 20–40% of patients. This was a mild and self-limited problem. Droperidol alone produced an increase in anxiety in approximately 20% of patients and also an increased frequency of restlessness. The effects were noted to a lesser extent when diazepam was added to droperidol.

The frequency of other side-effects for all drugs and combinations was small.

DISCUSSION

A decrease of anxiety during the period before operation is a desired function of premedication. It has been established in several studies that droperidol may actually cause an increase in anxiety in a certain number of patients when used alone (Morrison, 1970; Morrison, Clarke and Dundee, 1970; Ellis and Wilson, 1972) or in combination with a narcotic (Conner et al., 1978). Although it might seem that a drug which produces such an effect would not be used frequently by physicians, droperidol is a popular premedicant and has been found to rate highly with physicians (Stephen, 1970). Our study helps to illuminate this paradox.

The contrast between diazepam and droperidol when used alone is striking. A 10-mg dose of diazepam provides good relief of anxiety and sedation and would be taken again by 90% of patients. Droperidol, while providing better relief of anxiety and sedation scores at 32 min, would be taken again by only slightly more than half the patients. From the standpoint of the physician, the opposite result was obtained in that droperidol was chosen consistently over diazepam.

A careful review of the data which included comments by both patients and physicians suggests an explanation. The majority of physicians who did not rate diazepam highly felt the patients were too alert. The mean time for the rating by the physician was 58 min following administration of the premedication. From the sedation curves it can be seen that the effect of diazepam is on the decline at 32 min, while that of droperidol is increasing or peaking.

The most frequent reason given by patients for not wishing to receive droperidol again was that it increased their anxiety. This effect was noted in 20% of patients before operation. Some patients stated that they felt unable to express their anxiety while under the influence of the drug. A smaller number complained they had little or inadequate effect from the drug.

Increased anxiety was noted most frequently shortly following injection of the droperidol. Often the sedation scores were high by 32 min. It appears likely that patients who were initially anxious may have been too sedated to complain at the time they were rated by the physician. The implication of this for clinical practice is clear: without follow-up on the day after surgery, the undesirable effects of medication may be missed.

The frequency of increased anxiety before operation was the same for both doses of droperidol when used alone. The large 10-mg dose was chosen to exclude the possibility that this phenomenon was related to small concentrations of drugs. The overall frequency of increased anxiety was greater than these figures show because additional patients reported increased anxiety when interviewed after operation.

The addition of diazepam to droperidol did decrease the frequency of the increase in anxiety. Increase in anxiety was reported by 13% who received the diazepam 5 mg–droperidol combinations. Five per cent reported this occurrence with the diazepam 10 mg–droperidol combinations. Only one patient reported this in the group receiving diazepam 10 mg plus droperidol 2.5 mg.

While we did not study the effects of droperidol i.m., our results are similar to those of Ellis and Wilson (1972) who studied the effect of droperidol 5 mg with atropine 0.4 mg i.m. and reported a 40% frequency of increased anxiety.

Patients receiving the combinations did not appear aware of their surroundings in the preoperative area and the majority were sleeping. The degree to which they were able to be aroused to answer questions and look at the memory cards varied considerably. Four patients who received diazepam 10 mg plus droperidol 5 mg were unrousable for varying periods. About half the group was thought to be difficult or impossible to arouse during the first 30 min. While there were no changes in vital signs or untoward consequences, they were thought to be over-sedated. Only five patients receiving diazepam 5 mg and droperidol 2.5 mg were thought to be difficult to arouse and none was rated as over-sedated.

We did not adjust doses to patient size and most instances of over-sedation occurred in small patients. This possibility could be avoided in clinical practice by adjusting the dose to patient size. There is little advantage in using more than the smallest (2.5-mg) dose of droperidol in adults of average size. Diazepam 5 mg in combination with droperidol 2.5 mg is adequate for many patients, with the greater, 10-mg, dose of diazepam being reserved for larger patients or those with inadequate response to the smaller dose.

Droperidol is thought to work by blocking dopaminic pathways, an action not shared by diazepam which produces its sedative effects primarily by affecting the limbic system (Dundee and Wyant, 1974). It is interesting that combining moderate doses of either drug produces such potent effects. This suggests that other combinations of tranquillizers and sedatives with differing modes of action may lead to valuable interactions producing effects difficult to obtain with either drug alone.

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LE DIAZEPAM ET LE DROPERIDOL EN TANT QUE PREMEDICATIONS INTRAVEINEUSES

RESUME

Les effets du diazépam et du dropéridol administrés par voie intraveineuse, seuls ou ensemble, en tant que prémédication ont été étudiés sur 240 malades. On a procédé à une estimation du soulagement de l'anxiété, de la sédation, du manque de souvenir, de l'acceptation aussi bien par le malade que par le médecin, ainsi qu'à celle des effets secondaires. Dans l'ensemble, le mélange de dropéridol à raison de 2,5 mg et de diazépam à raison de 5 mg a donné de meilleurs rapports de ces éléments variables que ceux l'on a pu obtenir soit avec le dropéridol seul à raison de 10 mg, soit avec le diazépam seul aussi à raison de 10 mg. De plus fortes doses de dropéridol contenant du diazépam produisent une augmentation de la fréquence de l'anxiété, alors que de plus fortes doses de diazépam contenant du dropéridol peuvent provoquer un excès de sédation.

DIAZEPAM UND DROPERIDOL ALS INTRAVENÖSE VORBEHANDLUNGSMITTEL

ZUSAMMENFASSUNG

Die Wirkungen von intravenos verabreichtem Diazepam und Droperidol, sowohl allein als kombiniert, als Vorbehandlung, wurden bei 240 Patienten studiert. Beruhigung, Sedierung, Gedächtnisverlust, Akzeptierung durch Patienten und Arzte, sowie Nebenerscheinungen wurden untersucht. Allgemein ergab die Kombination von 2,5 mg Droperidol mit 5 mg Diazepam dabei bessere Ergebnisse als mit 10 mg Droperidol allein oder 10 mg Diazepam allein. Grossere Dosen von Droperidol mit Diazepam ergaben ein haufigeres Auftreten von Nervositat; grossere Dosen von Diazepam mit Droperidol konnten übermassige Sedierung bewirken.

DIAZEPAM Y DROPERIDOL COMO PREMEDICACION I.V.

SUMARIO

En 240 pacientes, se estudiaron los efectos del diazepam y del droperidol administrados i.v., ya sea cada uno por separado, ya sea en combinación, como premedicación. Se evaluaron el alivio de la ansiedad, la sedación, la falta de memoria, la aceptación por ambos paciente y médico, así como los efectos colaterales. En general, la combinación de 2,5 mg de droperidol con 5 mg de diazepam arrojaba mejores calibraciones de dichas variables que las que pudieron obtenerse con cualquiera de los dos productos, ya sea con 10 mg de droperidol solo, ya sea con 10 mg de diazepam. Cuando se administraron mayores dosis de droperidol con diazepam, se registraron una mayor frecuencia de ansiedad; mayores dosis de diazepam con droperidol pueden ocasionar una sobre-sedación.

Br. J. Anaesth. (1979), **51**, 543

PLASMA FENTANYL CONCENTRATIONS AND CLINICAL OBSERVATIONS DURING AND AFTER OPERATION

H. J. McQuay, R. A. Moore, G. M. C. Paterson and A. P. Adams

SUMMARY

Thirty patients undergoing major abdominal gynaecological surgery were anaesthetized with a standard technique including nitrous oxide in oxygen and myoneural blockade. The lungs were ventilated with large tidal volumes (10 ml kg^{-1}) but Pa_{CO_2} remained within normal limits. Fentanyl was given as a loading dose of 10 μg kg^{-1} or 25 μg kg^{-1} i.v. at the start of the anaesthetic. The lower dose was followed by either an infusion of fentanyl 2 μg min^{-1} or by fentanyl given as increments of 100 μg after 30 min and 50 μg after 1 h. Significant (2% level) second peaks of plasma fentanyl (increases greater than 0.49 ng ml^{-1}) occurred within 45 min of the end of surgery in 60% of patients receiving the infusion, in 40% of patients receiving the high dose and in 20% of patients receiving increments of fentanyl. Analgesia was required in the first 3 h after operation in 70% of patients in the infusion group, in 60% in the high dose group and in 80% in the increment group. The mean times for administration of postoperative analgesia in these three groups were 102, 80 and 55 min respectively. After operation Pa_{O_2} was less than 8 kPa in 60–67% of patients. It is suggested that particular care should be given to patients who are breathing air and recovering from anaesthesia in which fentanyl in large or recurring amounts has been used, since administration of analgesics after operation may produce additive effects and further arterial hypoxaemia.

Fentanyl is sometimes preferred to other opiates in balanced anaesthesia because of its rapidity of onset and brevity of action. Nevertheless, the duration of respiratory depression following the use of fentanyl has caused concern. Becker and others (1976) showed that recovery from respiratory depression associated with fentanyl anaesthesia followed a biphasic course and Adams and Pybus (1978) cited three patients in whom postoperative respiratory depression followed the use of fentanyl.

We have investigated the concentrations of fentanyl in the plasma during and after surgery to ascertain whether a biphasic or second peak effect occurs. The study also considers the effects of three modes of i.v. administration of fentanyl on the clinical conditions of the patients in the period after operation.

PATIENTS AND METHODS

The design of the trial was prospective and sequential. Informed consent was obtained from 30 healthy women undergoing major gynaecological surgery, usually hysterectomy through a transverse lower abdominal incision (table I).

Ten patients were investigated in each of three groups. A 0.53-mm i.d. cannula was inserted into the radial artery and an i.v. infusion of 500 ml of Hartmann's solution was established in one arm under local analgesia before general anaesthesia was induced. All patients received thiopentone 4 mg kg^{-1} and pancuronium 0.1 mg kg^{-1} and after tracheal intubation the lungs were ventilated with 33% oxygen in nitrous oxide. The East Radcliffe ventilator was adjusted to produce an expired tidal volume (measured at the catheter mount) of 10 ml kg^{-1} and respiratory frequency of 13 b.p.m. Ventilation at a constant Pa_{CO_2} between 4.7 and 4.9 kPa was achieved using a Penlon version of the Bain co-axial anaesthetic breathing circuit using a total flow of fresh gases of 75 ml kg^{-1}. Increments of pancuronium 0.02 mg kg^{-1} were given after 40 min and repeated if clinically indicated.

Group A received no premedication; however, vascular cannulation was sometimes difficult because of vasoconstriction and so the patients in the later groups B and C received diazepam 10 mg orally 2 h before operation.

A loading dose of fentanyl 10 μg kg^{-1} (groups A and B) or 25 μg kg^{-1} (group C) was given i.v. with the induction of anaesthesia.

Group A received an infusion of fentanyl 2 μg min^{-1} beginning 20 min after the induction of anaesthesia.

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The infusion technique was used to achieve a steady-state concentration of fentanyl in the plasma. The infusion was continued into the recovery period for 30 min from the end of surgery during which time the patient breathed spontaneously; the decay in plasma fentanyl when the infusion was discontinued could then be observed independently of the other anaesthetic factors.

Group B received additional fentanyl in the form of two i.v. increments, 100 μg at 30 min and 50 μg at 60 min after the initial loading dose. The dose at 60 min was omitted in three of the patients in this group because the operation had been completed.

Group C received no additional fentanyl after the initial loading dose.

Arterial pressure, heart rate, body temperature and e.c.g. were monitored during operation and recovery.

At the end of surgery the anaesthetic gases were withdrawn and residual neuromuscular block was antagonized by neostigmine 2.5 mg and atropine 1.2 mg i.v. Each patient was observed for 3 h in the recovery room where the same observer noted the clinical signs of ventilation and general condition and administered pain relief. Papaveretum 15 mg i.m. was given in response to either a complaint of pain or a request for analgesia by the patient.

Samples of arterial blood were analysed for pH, $P\text{CO}_2$ and $P\text{O}_2$ during the operation and at 10, 20, 45, 90 and 180 min after operation using a Radiometer ABL 1 blood-gas system.

Fentanyl and cortisol assays

Plasma fentanyl concentrations were measured by a modification of the radioimmunoassay method (Michiels, Hendriks and Heykants, 1977). The modification required only 50 μl of plasma and the addition of 500 μl of buffer. Larger amounts of plasma as recommended in the original method were found to give bizarre, non-specific binding effects which were obviated by using a smaller volume of plasma; quenching effects were also minimized in this way. The coefficient of variation of the measurement within assays was 3.8% and between assays it was less than 10%. Michiels, Hendriks and Heykants (1977) have shown that the known metabolites of fentanyl, even in large amounts, do not interfere with the radioimmunoassay of fentanyl because of their much reduced binding affinities to the antiserum. Plasma cortisol was measured by a competitive protein binding assay modified by the use of Sephadex instead of Florisil (Murphy, 1976). The within-assay and between-assay coefficient of variation of the measurement was less than 10%.

Sampling times

Blood samples for fentanyl assay were taken at various times during anaesthesia and surgery and in the period after operation.

In group A samples were taken at 5 and 15 min after the initial loading dose of fentanyl and at 15 and 30 min after the end of anaesthesia when the residual

TABLE I. *Patient data for the three groups, means ± SEM. Ranges in parentheses*

	Group		
	A. Infusion	B. Increment	C. High dose
Age (yr)	43.9 ± 3.9 (32–75)	39.9 ± 1.3 (33–48)	39.8 ± 2.5 (27–54)
Weight (kg)	72.2 ± 3.9 (59–90.6)	62.9 ± 3.8 (47–91)	58.7 ± 3.0 (44.5–75)
Initial dose of fentanyl ($\mu\text{g kg}^{-1}$)	10	10	25
Maintenance dose of fentanyl	Nil for 20 min, then 2 $\mu\text{g min}^{-1}$ infusion until 30 min after end of anaesthesia	100 μg at 30 min (all patients); 50 μg at 60 min (7 patients)	Nil
Mean dose of fentanyl ($\mu\text{g kg}^{-1}$)	12.7 ± 0.3	12.1 ± 0.2	25
Mean total dose of fentanyl (μg)	918 ± 84	760 ± 40	1467 ± 75
Duration of anaesthesia (min)	88 ± 11 (43–139)	96 ± 7 (65–110)	113 ± 7 (80–145)
Intra-operative Pa_{CO_2} (kPa)	4.70 ± 0.17	4.90 ± 0.20	4.68 ± 0.19

neuromuscular block was antagonized and while the fentanyl infusion was continuing. In the period after surgery further samples were taken at 5, 10, 20, 45, 90 and 180 min after the fentanyl infusion was stopped. Since the infusion continued for 30 min after the operation these times represent 35, 40, 50, 75, 120 and 210 min from the end of surgery.

In group B samples were taken 5 and 25 min after the loading dose of fentanyl and 5 and 25 min after the 100-μg increment and 5 min after the 50-μg increment of fentanyl. Further samples were taken at 10, 20, 45, 90 and 180 min from the end of the operation.

In group C samples were taken at 5 and 15 min after the loading dose of fentanyl and then every 15 min until the end of surgery. Further samples were taken at 10, 20, 45, 90 and 180 min from the end of the operation.

The duration of anaesthesia and surgery varied slightly between the three groups. The mean time of operation was longest in group C (table I).

RESULTS

The mean doses related to weight and total doses of fentanyl for each of the three groups are shown in table I.

Figure 1 shows the 10 individual plots of plasma fentanyl against time from the initial dose of 25 μg kg^{-1} in group C. Examination of individual plots shows significant second peaks in plasma fentanyl in four of the 10 patients in this group. An increase in plasma fentanyl of more than 0.49 ng ml^{-1} from the previous value is taken to constitute a second peak at the 2% level of significance. In the other two groups significant second peaks occurred in six of the 10 patients in group A and two of the 10 in group B. The occurrence of all these second peaks was within 45 min of the end of surgery.

The changes in mean plasma fentanyl concentrations at each sampling time are shown in figures 2–4. In these figures the increases in plasma fentanyl which tended to occur in individual patients within 45 min of the end of surgery are flattened because the duration of operation varied between patients (table I). However, the absence of the expected exponential type of curve following fentanyl administered i.v. in these experiments, and the persistence of plasma fentanyl concentrations above such expected responses, are evident. The decay in plasma fentanyl concentrations following the end of surgery is shown in table II.

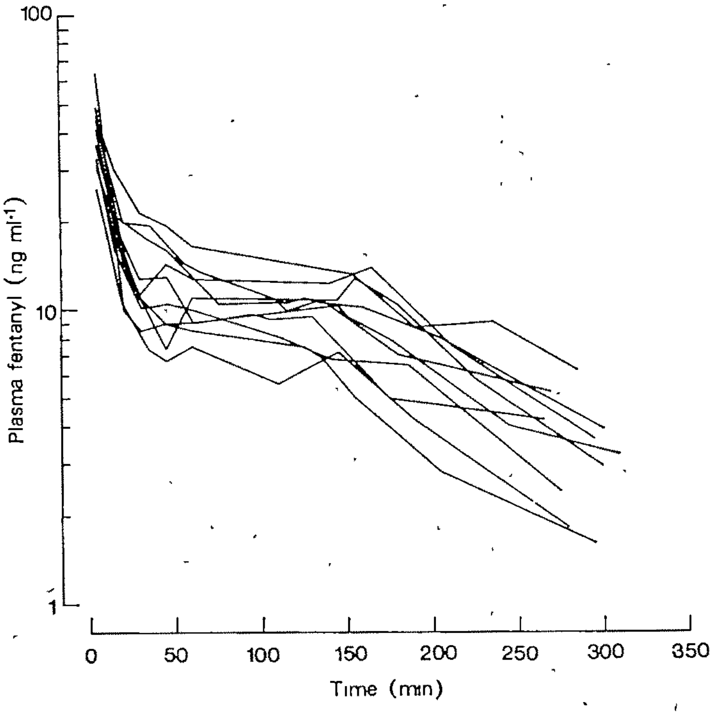

FIG. 1. Plasma fentanyl concentrations in the 10 patients (group C) receiving an i.v. loading dose of fentanyl 25 μg kg^{-1}.

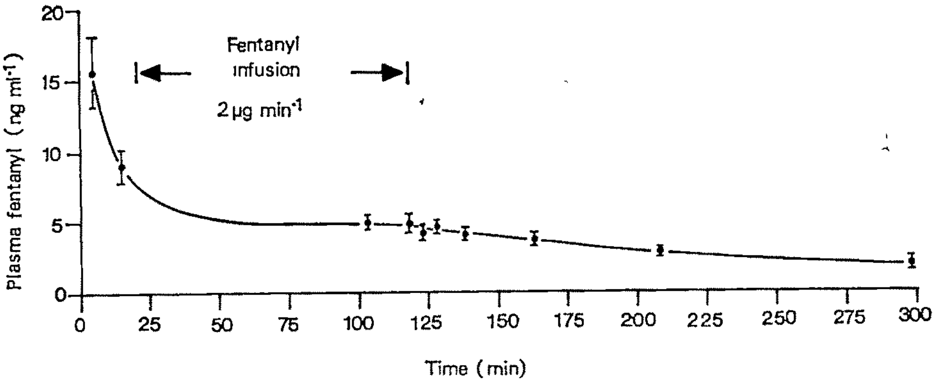

FIG. 2. Plasma fentanyl concentrations (means ± SEM) in the 10 patients in group A (infusion group).

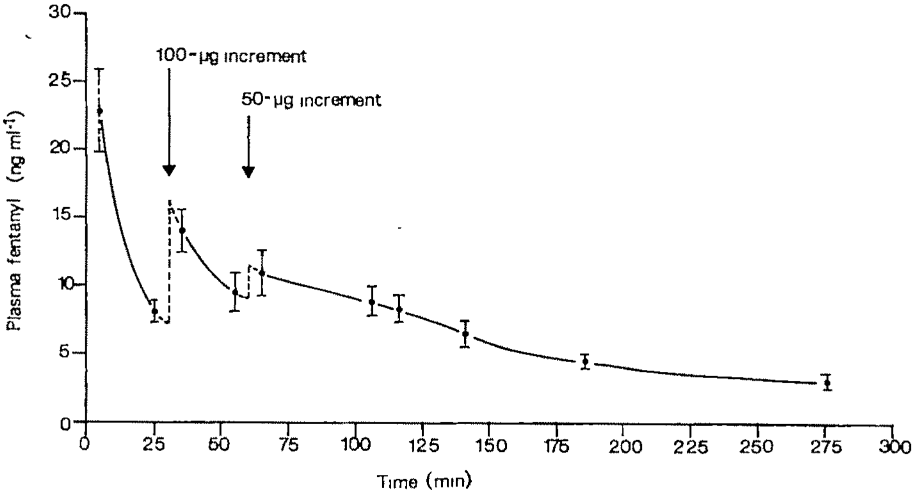

FIG. 3. Plasma fentanyl concentrations (means ± SEM) in the 10 patients in group B (increment group).

TABLE II. *Postoperative plasma fentanyl concentrations (ng ml^{-1}) (means ± SEM). Ten patients in each group. *Time from end of infusion in group A*

Time from end of op. (min)*	Group		
	A. Infusion	B. Increment	C. High dose
10	4.08 ± 0.53	8.76 ± 1.20	9.94 ± 0.72
20	4.29 ± 0.41	8.19 ± 1.02	9.73 ± 0.72
45	3.80 ± 0.45	6.40 ± 0.72	9.10 ± 0.80
90	3.01 ± 0.48	4.48 ± 0.57	6.23 ± 0.74
180	2.01 ± 0.32	3.09 ± 0.49	3.94 ± 0.64

Plasma cortisol concentrations

Administration of fentanyl by three different dose regimes in these studies failed to obtund the increase in plasma cortisol concentrations normally associated with the stress of anaesthesia and surgery (table III).

Pain following surgery

The percentages of patients complaining of pain or requesting pain relief during the first 3 h after surgery were 70% in group A, 80% in group B and 60% in group C. The latency before analgesia was required was 102 (± 25 SEM) min, 55 (± 18 SEM) and 80 (± SEM) min from the end of surgery in groups A, B and C respectively.

Blood-gases after operation

In two patients in group A, three in group B and two in group C Pa_{O_2} was less than 8 kPa in the first 3 h after surgery. However, cyanosis was noted in a further 11 patients (four in group A, three in group B and four in group C) and oxygen-enriched air was given to these patients to breathe without awaiting the results of blood-gas analysis. These figures do not

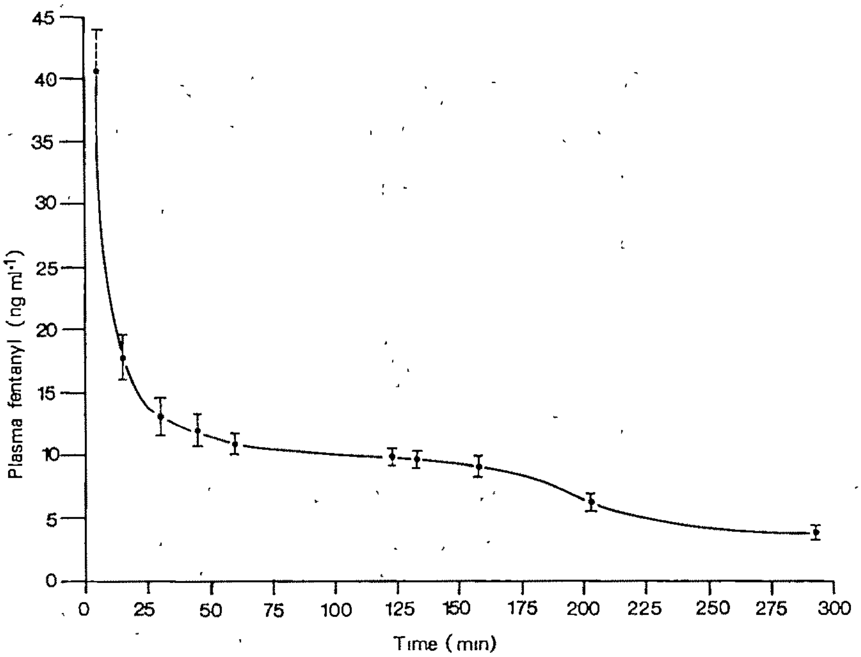

FIG. 4. Plasma fentanyl concentrations (means ± SEM) in the 10 patients in group C (high dose group).

TABLE III. *Plasma cortisol concentrations (nmol litre*$^{-1}$*) (means ± SEM)*

Group	Time from induction of anaesthesia (min)				
	0	60	120	210	300
A. Infusion	406 ± 63	not available	892 ± 47	1037 ± 73	1110 ± 77
B. Increment	422 ± 84	708 ± 101	866 ± 105	894 ± 93	1041 ± 134
C. High dose	335 ± 19	571 ± 62	706 ± 128	845 ± 106	955 ± 106

include patients who were given analgesia in the period after operation. Hence 66.6% of patients in each of groups A and B and 60% of patients in group C gave cause for concern.

The greatest increase in mean Pa_{CO_2} after operation occurred at 10 min in groups B and C (Pa_{CO_2} 5.70 kPa and 5.76 kPa respectively) and at 20 min in group A (Pa_{CO_2} 6.36 kPa).

DISCUSSION

The plasma concentrations of fentanyl obtained in these experiments are in broad agreement with the values obtained by Hess, Stiebler and Herz (1972) who used radiolabelled fentanyl in rabbits, two human volunteers and three gynaecological patients. They showed that there was a slower metabolism of fentanyl in man than in the rabbit and that redistribution played a dominant role in man. Indeed, it seems forgotten that Hess, Stiebler and Herz (1972) warned, more than 6 years ago, that particular care should be taken after several consecutive injections of fentanyl.

Becker and colleagues (1976) found that the carbon dioxide response curves in anaesthetized patients were at their lowest 2.5 h after the last dose of narcotic and approximately 1 h after the patients entered the recovery room; the greatest end-tidal $P\text{CO}_2$ values after operation also occurred at about this time. They pointed out that the potential risk is camouflaged by a relatively normal end-tidal $P\text{CO}_2$ even though the patient's carbon dioxide response is depressed.

Carbon dioxide ventilatory responses in awake man show that fentanyl displaces the curve to the right. However, with loss of consciousness a different effect is seen—a consistent decrease in slope of the response and an unpredictable and inconsistent effect on its displacement. Harper and colleagues (1976) studying volunteers demonstrated dose-related depression of the carbon dioxide response curve by various doses of fentanyl administered i.v. Although the respiratory depression was maximal at 5 min the slope did not return to control for 2 h and the shift to the right of the curve persisted for 4 h. The greatest doses of fentanyl used in that study were comparable to those used in the present study and the $P_{15}CO_2$ responses, which gave the most consistent results, had not returned to 10% of control value until 3 h after the administration of fentanyl. The respiratory effects of fentanyl may indeed persist, depending on dose, for 3–4 h (Downes, Kemp and Lambertsen, 1967; Dunbar et al., 1967; Harper et al., 1976; Rigg and Goldsmith, 1976). When more than one dose of fentanyl has been given an extended effect is seen, presumably as a result of cumulation (Kay and Rolly, 1977). The mean loading dose of 268 μg used in those studies lasted 35 min, as judged by clinical signs of inadequate analgesia during surgery, but two or three increments of 67 μg extended the overall action to just over 90 min.

The authors have shown a statistically significant second peak of fentanyl in the plasma in many of the patients in all three groups studied. It is of interest that this effect appeared within about 45 min of the end of the operation. It is within such time that consciousness is regained and muscle tone, body temperature and voluntary movements return. However, it is not clear whether this second peak has clinical significance.

Any potentially harmful effects from respiratory depression may be counteracted by varying degrees of stimulation after operation. The respiratory depression following surgery in the patients reported by Adams and Pybus (1978) may be associated with such lack of stimulation, although the event was delayed much longer than the time at which second peaks of fentanyl were observed in the plasma in the present investigation. It is possible that the effects may have been compounded by the usual opiate premedication which was given; however, other data suggest that pethidine has no residual effects (Tigerstedt, 1977). Vejlsted, Hansen and Jacobsen (1977) found that pethidine used as premedication for patients undergoing neuroleptanaesthesia with fentanyl 420 μg in divided doses was associated with respiratory depression lasting up to 6 h. It is also possible that fentanyl concentrations in the central nervous system are relatively great at this time. Pentazocine and morphine concentrations in plasma and brain follow classical pharmacokinetic theory in animal experiments (Pittman and Portman, 1974; Dahlström and Paalzow, 1975). However, the pharmacokinetics of pethidine differ in anaesthetized man and awake man; it is suggested that the disposition kinetics of pethidine are largely perfusion-controlled (Mather et al., 1976). The present study shows that after the i.v. administration of fentanyl the concentrations of drug in the plasma decay very rapidly; thereafter, there is a slower decline followed by a period of stabilization and then plasma concentrations decrease very slowly. The decay in plasma fentanyl does not follow an exponential curve, and the concentrations of drug are greater than would be expected from such a relationship. These findings are in agreement with those recently reported by Schleimer and colleagues (1978). Although these workers did not specifically report on biphasic plasma fentanyl concentrations it is possible that this phenomenon did occur but was obscured by the averaging of the results. Averaging was necessary, however, because of the fluctuations in individual serum fentanyl concentrations found at later sampling times. Similarly, in the present study, examination of individual dose–time responses to fentanyl was necessary to detect the biphasic response. Schleimer and colleagues (1978) relate their findings to a three-compartment model comprising a central compartment of blood and some extravascular locations, and two tissue compartments each with a different rate of uptake and release of the drug. They were able to detect fentanyl in the serum for at least 6 h after administration of the drug. In the present study rapid decrease in plasma concentrations of fentanyl would be expected when the fentanyl infusion in group A patients was stopped. At the plateau fentanyl enters and leaves the circulation at a rate of 2 μg min^{-1}. When the infusion was stopped the mean rate of decrease of concentration of fentanyl was 370 μg min^{-1}/ml plasma or 1.85 ng ml^{-1} in the first 5 min. If the decay was exponential smaller values would be expected, but the mean plasma concentration was only 0.7 ng ml^{-1} after 5 min and still only 0.7 ng ml^{-1} after 20 min.

A disconcerting finding in the period after operation was that many of the patients studied had low Pa_{O_2} values despite having received neither postoperative analgesia nor opiate premedication. The hypoxaemia following atropine premedication (Conway, 1975) or a hypocapnic anaesthetic technique (Salvatore, Sullivan and Papper, 1969) can be excluded. In the present study all the patients received normocapnic ventilation with large tidal volumes. It would appear that this hypoxaemia was not a result of uncomplicated respiratory depression because arterial $P\mathrm{co}_2$ values were not increased markedly (table I). The cause is probably a result of mismatching between ventilation and perfusion in the lung which may be a result of reduced functional residual capacity with airway closure, or reduced total pulmonary compliance.

The three methods of administering fentanyl during anaesthesia were disappointing in the amount of useful analgesia which could be carried over into the period after operation. The high single-dose method appears marginally better than the conventional incremental dose method used by many anaesthetists, but the increased duration of analgesia following the infusion is hardly likely to merit routine acceptance considering the complexity and inherent dangers associated with such a technique. Although the clinical conduct of anaesthesia was entirely satisfactory in all patients, the suppression of the stress response to surgery by fentanyl in the dosages used was not confirmed by serial plasma cortisol assays. This finding is in contrast to that reported by Hall and others (1978) for a group of patients receiving a bolus injection of fentanyl 50 mg kg^{-1} at the start of anaesthesia; we are unable to account for this difference.

These findings confirm warnings that particular attention should be paid to ensure adequate oxygenation in the period after operation especially if further analgesia is needed. It is no longer wise to regard fentanyl as a short-acting drug and the use of large or repeated doses may lead to respiratory problems after operation (Andersen, Doubloug and Refstad, 1976).

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CONCENTRATIONS DE FENTANYL DANS LE PLASMA ET OBSERVATIONS CLINIQUES PENDANT ET APRES L'INTERVENTION CHIRURGICALE

RESUME

Trente malades devant subir une intervention chirurgicale gynécologique majeure à l'abdomen ont été anesthésiés à l'aide d'une technique standard comprenant du protoxyde d'azote dans l'oxygène, ainsi qu'un blocage musculo-nerveux. Les poumons ont été ventilés par de grands volumes courants (10 ml kg^{-1}), mais la Pa_{CO_2} est restée dans les limites normales. Le fentanyl a été administré à une dose de charge de 10 µg kg^{-1} ou de 25 µg kg^{-1} au début de l'anesthésie. La plus faible dose a été suivie soit d'une infusion de fentanyl (2 µg kg^{-1}), soit de fentanyl administré par paliers de 100 µg après 30 min et de 50 µg après 1 h. Il s'est produit dans les 45 min qui ont suivi l'intervention, et ce dans 60% des cas pour les malades qui avaient reçu l'infusion, dans 40% des cas qui avaient reçu la forte dose et enfin dans 20% des cas ou les malades avaient reçu du fentanyl par paliers, des crêtes importantes (2%) de fentanyl dans le plasma (augmentations supérieures à 0,49 ng ml^{-1}). Il fallait que l'analgésie dure pendant les trois premières heures suivant l'intervention, dans 70% des cas du groupe ayant reçu l'infusion, dans 60% des cas de celles ayant reçu la forte dose et dans 80% de celles ayant reçu le médicament par paliers. Les durées moyennes pour l'administration de l'analgésique post-opératoire dans ces trois groupes ont été respectivement de 102, 80 et 55 min. Après l'opération, la Pa_{O_2} a été inférieure à 8 kPa dans 60 à 67% des cas. Nous recommandons que l'on prenne un soin tout particulier des malades qui respirent de l'air et qui récupèrent de l'anesthésie provoquée par de fortes doses de fentanyl, ou par des doses administrèes par palier, du fait que l'administration d' analgésiques aprés l'intervention chirurgicale peut provoquer des effets supplémentaires et entre autres une hypoxémie artérielle.

PLASMA-FENTANYL-KONZENTRATIONEN UND KLINISCHE BEOBACHTUNGEN WAHREND UND NACH DER OPERATION

ZUSAMMENFASSUNG

Dreissig Patienten wurden vor grösseren gynäkologischen Operationen durch ein Standardmethode narkotisiert—mit Stickoxyd in Sauerstoff und myoneuraler Blockierung. Die Lungen wurden mit grossen Atemvolumen (10 ml kg^{-1}) beluftet, doch bleib Pa_{CO_2} innerhalb normaler Grenzen. Fentanyl wurde in einer Dosis von 10 µg kg^{-1} oder 25 µg kg^{-1} intravenos bei Beginn der Narkose verabreicht. Der niedrigeren Dosis folgte entweder eine Infusion von 2 µg min^{-1}, oder Fentanyl in steigenden Dosen von 100 µg nach 30 min oder 50 µg nach 1 Stunde. Wesentliche (2%) Spitzen von Plasma-Fentanyl (Anstiege uber 0,49 ng ml^{-1}) entstanden innerhalb von 45 min nach der Operation bei 60% der Patienten; die die Infusion erhalten hatten, bei 40%, die die grosse Dosis erhalten hatten, und bei 20%, die die steigenden Dosen erhalten hatte. Analgesie in den ersten 3 Stunden nach der Operation war bei 70% der Patienten der Infusionsgruppe erforderlich, bei 60% in der Gruppe mit grosser Dosis, und bei 80% in der Gruppe mit steigender Dosis. Die Zeit der Verabreichung postoperativer Analgesie betrug bei den drei Gruppen jeweils durchschnittlich 102, 80 und 55 min. Nach der Operation lag Pa_{O_2} bei 60–67% der Patienten unter 8 kPa. Besondere Pflege sollte Patienten gewahrt werden, die Luft atmen und sich von einer Narkose erholen, in der Fentanyl in grossen oder wiederholten Dosen verwendet wurde, denn die postoperative Verabreichung von schmerzlindernden Mitteln kann additive Wirkungen haben und eine weitere arterielle Hypoxämie bewirken.

CONCENTRACIONES DE FENTANILO PLASMATICO Y OBSERVACIONES CLINICAS DURANTE LA OPERACION Y DESPUES DE ELLA

SUMARIO

Se administró la anestesia según una técnica normal, inclusive el óxido nitroso en oxigénico y el boqueo mioneural, a 30 pacientes en los cuales estaba por practicarse operaciones quirúrgicas ginecológicas abdominales mayores. Se ventilaron los pulmones con grandes volúmenes de aire respiratorio (10 ml kg^{-1}), pero el Pa_{CO_2} permaneció dentro de los límites normales. Se administró el fentanilo como dosis cargadora de 10 µg kg^{-1} ó 25 µg kg^{-1} i.v. al principio de la anestesia. La dosis más reducida fue seguida ya sea por una infusión de fentanilo (2 µg min^{-1}) ya sea por fentanilo administrado como incrementos de 100 µg después de 30 min y de 50 µg después de 1 h. Se produjeron ápices secundarios significativos (nivel del 2%) de fentanilo plasmático (aumentos superiores a 0,49 ng ml^{-1}) dentro de 45 min después de fin de la operación en un 60% de los pacientes que recibieron la infusión, en un 40% de los que recibieron la dosis alta y en un 20% de los que recibieron los incrementos de fentanilo. La analgesia fue necesaria durante las primeras tres horas después de la operación en un 70% de los pacientes del grupo de infusión, en un 60% de los del grupo de dosis alta y en un 80% de los del grupo de incrementos. Los tiempos de administración de analgesia postoperatoria en estos tres grupos fueron de 102, 80 y 55 min, respectivamente. Después de la operación, el Pa_{O_2} era inferior a 8 kPa en un 60 a 67% de los pacientes. Se sugiere tener un cuidado particular con los pacientes que respiran aire y se recuperan de la anestesia cuando se usaron cantidades mayores o recurrentes de fentanilo, puesto que la administración de analgésicos después de la operación puede producir efectos aditivos e hipoxemia arterial ulterior.

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CARDIORESPIRATORY CHANGES FOLLOWING INDUCTION OF ANAESTHESIA WITH ETOMIDATE IN PATIENTS WITH CARDIAC DISEASE

M. P. Colvin, T. M. Savege, P. E. Newland, E. J. M. Weaver, A. F. Waters, J. M. Brookes and R. Inniss

SUMMARY

The cardiorespiratory effects of etomidate were measured in two groups of six patients with aortic or mitral valve disease. The induction of anaesthesia with etomidate 0.3 mg kg^{-1} was followed by a second dose 10 min later. After the first dose, a 19% decrease in systemic arterial pressure was associated with a decrease in systemic vascular resistance and left ventricular heart work. Cardiac index, pulmonary artery pressure and wedge pressure all decreased slightly. Central venous pressure and heart rate did not change. A slight increase in respiratory frequency failed to prevent an increase in Pa_{CO_2}. Changes after the second dose were similar. The two groups of patients did not differ significantly in their response to etomidate. No patient complained of pain during injection, nor did myoclonic movements occur.

Etomidate is associated with minimal changes in the cardiovascular system (Doenicke, Kugler et al., 1973; Doenicke, Wagner and Beetz, 1973; Holdcroft et al., 1976), and could be suitable for the induction of anaesthesia in patients with cardiac disease.

In this study, measurements were made of the cardiorespiratory changes that occurred during the induction of anaesthesia before cardiac surgery in patients with aortic or mitral valve disease. Since one dose at induction might reflect only the physiological changes associated with the onset of unconsciousness, a second identical dose of the drug was given 10 min after the first, but before the patient regained consciousness.

PATIENTS AND METHODS

All the patients in the study were about to undergo cardiac surgery and were divided into two groups. Six patients had predominantly aortic valve disease and six predominantly mitral valve disease (table I). Patients with obvious heart failure, angina or a resting systemic arterial pressure greater than 150/90 mm Hg were excluded.

TABLE I. *Details of patients (numerical values are mean ± SD)*

Diagnosis	No.	Age (yr)	Weight (kg)	Surface area (m^2)	Rhythm
Mitral valve disease	3M 3F	64 (±7.8)	61 (±7.8)	1.70 (±0.15)	All atrial fibrillation
Aortic valve disease	4M 2F	61 (±7.3)	64 (±6.2)	1.72 (±0.10)	All sinus rhythm
All patients	12	63 (±7.3)	62 (±6.9)	1.71 (±0.12)	

Premedication

At the visit before operation, the cannulation procedure was explained to the patient and written consent to use etomidate obtained. Papaveretum 0.3 mg kg^{-1} and promethazine 0.7 mg kg^{-1} i.m. were administered as premedication and, at the surgeon's request, digoxin 0.25 mg and antibiotics were given at the same time. In each group, three patients received ampicillin 250 mg and cloxacillin 250 mg and three received gentamicin 80 mg and flucloxacillin 250 mg.

Procedure

The patient was made comfortable on the operating table, the e.c.g. leads attached, a chest stethograph positioned and oxygen administered through an M.C. face mask.

Under local anaesthesia a Swan–Ganz catheter (7 f.g.) was positioned in the pulmonary artery via the

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right internal jugular vein, and the left femoral artery cannulated for measurement of arterial pressure. Details of the cannulation procedure have been described previously (Savege et al., 1976).

When the patient had rested for 15 min, control measurements were made over a 5-min period and during this time at least three values for cardiac output were determined. Anaesthesia was induced by the injection of etomidate 0.3 mg kg^{-1} i.v. over 60 s through an indwelling needle (19 f.g.) in the left hand. This dose had been recommended by the manufacturers and used in previous studies (Doenicke, Kugler et al., 1973; Morgan, Lumley and Whitwam, 1975; Holdcroft et al., 1976). After 10 min of measurement a second dose of 0.3 mg kg^{-1} was given over 60 s and measurement continued for a further 10 min.

Measurements, analysis and calculations

Systemic and pulmonary artery pressures, central venous pressure and, at 1-min intervals, pulmonary artery wedge pressure were recorded continously and were subsequently measured from the trace every 12 s. Groups of five readings in each minute were used to calculate "minute means".

Heart rate and respiratory frequency were counted from this continuous trace. Cardiac output was determined every 2 min by thermodilution using a Devices cardiac output computer. Blood-gas tensions were measured in all patients. After a control sample, further samples were taken 3, 6 and 9 min after the injection of each dose of etomidate.

Surface area, cardiac index, stroke index, mean arterial pressure, vascular resistance and ventricular minute work index were calculated from established formulae using a Hewlett–Packard 9810 A Calculator. Control values for the first injection were obtained over a 5-min period; control values for the second injection were those measured over the immediately preceding minute. The mean change in each variable was compared with the control value at 1-min intervals and tested for significance using Student's *t* test for correlated means.

A more detailed account of the method of obtaining measured and derived values can be found in a previous paper (Savege et al., 1976).

RESULTS

The physical and clinical details of the two groups of patients are shown in table I.

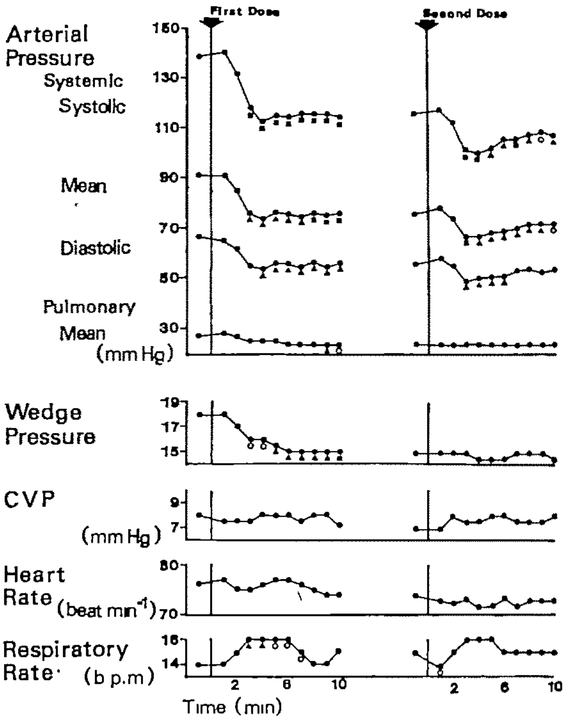

FIG. 1. Mean changes in measured cardiorespiratory variables in a group of 12 patients with cardiac disease. Each patient received etomidate 0.3 mg kg^{-1} over 30 s. This dose was repeated after 10 min. ■$P<0.001$; △$P<0.01$; ▲$P<0.02$; ○$P<0.05$.

Combined results for all 12 patients

Systemic arterial pressure (fig. 1, table II). There was a statistically significant decrease in systolic and diastolic pressures of 19% in the first 4 min following the first dose of etomidate. These pressures remained at this level until the second dose was given, when a further decrease of 13% occurred after 2 min. Thereafter the pressure recovered slightly.

Pulmonary artery pressure (fig. 1, table II). After the first dose there was a slow decrease in mean pulmonary artery pressure to a maximum of 11%. This was statistically significant only at 9 and 10 min. There was no change following the second dose.

There was a statistically significant decrease in pulmonary artery wedge pressure after 3 min by a maximum of 3 mm Hg. No further change occurred after the second dose.

Central venous pressure (CVP). There was no change in CVP after either dose.

Heart rate (fig. 1, table II). There was no significant change in heart rate after either dose. There were no alterations in cardiac rhythm.

Cardiac and stroke index (fig. 2, table II). After each dose, there were small decreases in cardiac index that were statistically significant 3 min after the first dose and 1 min after the second. The decrease in stroke index was even smaller and was not statistically significant.

TABLE II. *A comparison of the maximum percentage changes in cardiovascular variables following the administration of two doses of Althesin or etomidate to two groups of patients with cardiovascular disease. For each drug n = 12, drug injected over 60 s*

	Althesin* 0.05 ml kg^{-1}		Etomidate 0.3 mg kg^{-1}	
	1	2	1	2
Systemic arterial pressure				
Systolic	−21	−6	−19	−13
Diastolic	−18	−9	−19	−13
Pulmonary arterial pressure				
Mean	±7	−12	−11	0
Wedge (mm Hg)	−4.2	+1.1	−3	−1.4
CVP (mm Hg)	−1.2	−0.6	−0.5	+1
Heart rate	±3	±1	−2.6	−2.7
Cardiac index	−8	±5	−13	−10
Stroke index	−9	±6	−7	−3
Vascular resistance				
Systemic	−16	−12	−17	+23
Pulmonary	+39	+6	+27	+23
Ventricular minute work index				
Left	−23	−12	−27	−15
Right	−17	−11	−21	−12

*Savege and colleagues (1976).

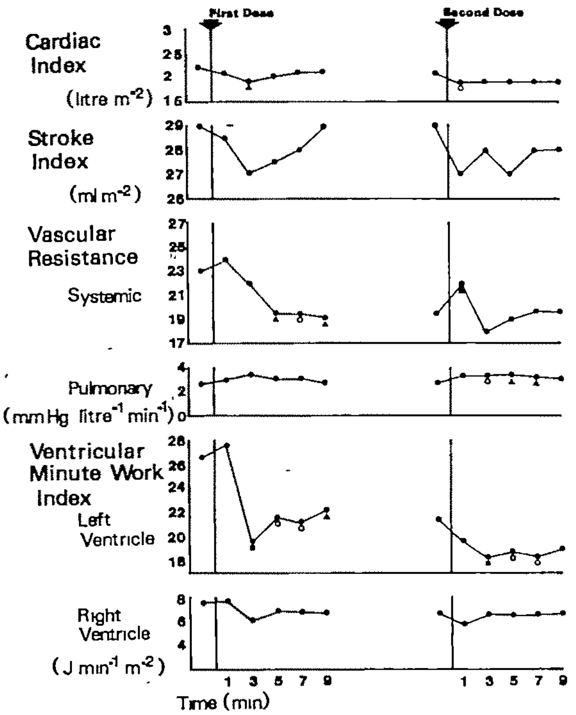

FIG. 2. Mean changes in calculated cardiovascular variables in a group of 12 patients with cardiac disease. (See legend for fig. 1.) ■$P<0.001$; △$P<0.01$; ▲$P<0.02$; ○$P<0.05$.

Systemic and pulmonary vascular resistances (fig. 2, table II). After the first dose, the systemic vascular resistance increased at 1 min and then decreased steadily by a maximum of 17% at 5 min; this decrease was statistically significant. After the second dose, the increase at 1 min was even more marked (+23%) and was statistically significant. Following this there was a marked decrease at 3 min but thereafter resistance recovered to the control value by 10 min; these changes were not statistically significant.

Pulmonary vascular resistance increased by 27% at 3 min and then decreased slowly to control. The absolute increase was small and not statistically significant. After the second dose the smaller increase of 23% was statistically significant and remained increased slightly until the end of the period of measurement.

Heart work (fig. 2, table II). After a small increase, left ventricular heart work decreased markedly and significantly at 3 min and thereafter there was a slow increase. Following the second dose there was a further decrease (15%) at 3 min, which was sustained.

Right ventricular work decreased slightly to a maximum at 3 min after each dose. It remained below control values for the rest of the recorded period.

Respiratory changes (fig. 1, table III). Following the first dose, respiratory frequency increased by two breaths per minute from the 3rd to the 6th minute. This increase was statistically significant.

After the second dose, the frequency decreased initially, but by the 3rd minute had increased again by 2 b.p.m.

Despite the small increase in respiratory rate, there was a statistically significant increase in Pa_{CO_2} after each dose. Pa_{O_2} did not change.

Other effects of etomidate. In all patients etomidate produced a rapid onset of anaesthesia. There were no

TABLE III. *Arterial* P_{O_2}, P_{CO_2} *and pH in 12 patients receiving etomidate (mean ± SD) and breathing oxygen by mask*

		Dose 1				Dose 2		
	Control	3 min	6 min	9 min	Control	3 min	6 min	9 min
pH (unit)	7.37 (±0.05)	7.33* (±0.04)	7.34* (±0.04)	7.34* (±0.04)	7.34 (±0.04)	7.31* (±0.05)	7.32* (±0.04)	7.32* (±0.04)
Pa_{CO_2} (kPa)	5.6 (±1.1)	6.4* (±0.7)	6.4* (±0.7)	6.1 (±0.7)	6.1 (±0.7)	6.8* (±0.9)	6.7* (±0.9)	6.5* (±0.8)
Pa_{O_2} (kPa)	20.1 (±6.1)	19.5 (±8.6)	19.7 (±8.2)	19.6 (±7.8)	19.5 (±7.8)	18.8 (±7.8)	20.1 (±7.3)	20.4 (±7.4)

$^*P < 0.02$.

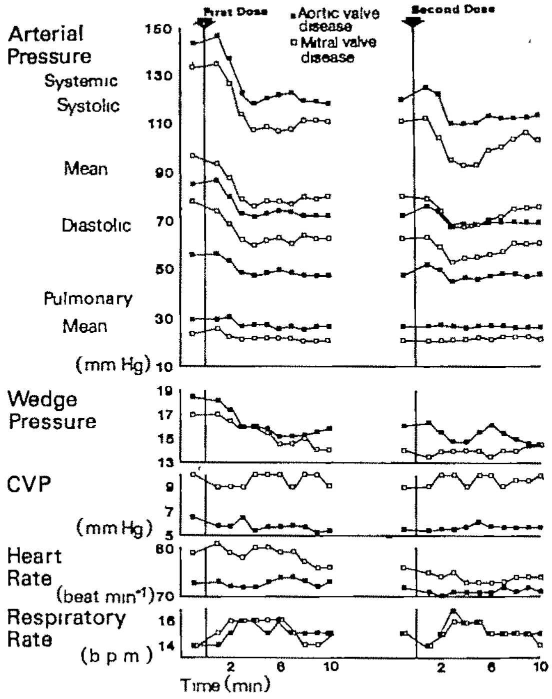

FIG. 3. Mean changes in measured cardiorespiratory variables in two groups of patients, six with aortic valve disease and six with mitral valve disease. (See legend for fig. 1.)

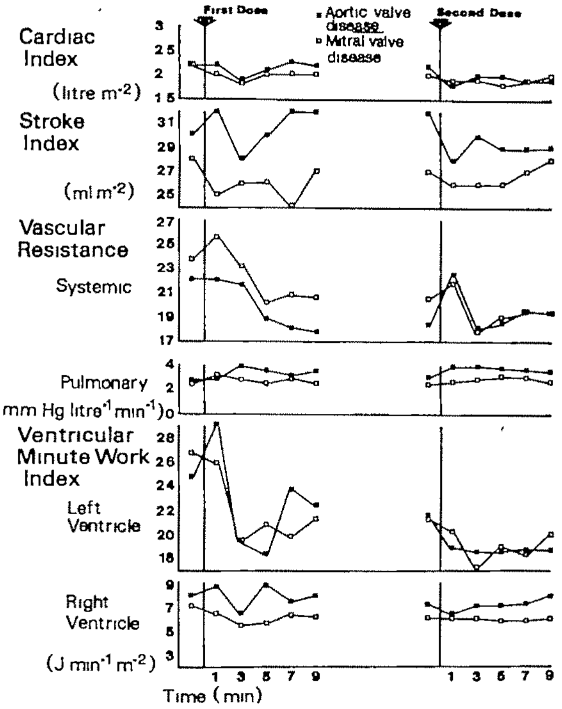

FIG. 4. Mean changes in calculated cardiovascular variables in two groups of patients, six with aortic valve disease and six with mitral valve disease. (See legend for fig. 1.)

instances of involuntary movements during induction.

Despite the fact that the drug was injected into a vein in the back of the hand, no patient complained of pain during the injection of the drug.

Results separated into aortic and mitral groups

Figures 3 and 4 show how the 12 patients behaved when divided into the groups with predominantly aortic or mitral valve disease. Although the control values of the two groups often differed widely and the systemic arterial diastolic pressure of the aortic group was predictably less than in the mitral group, both groups responded similarly.

DISCUSSION

Previous investigations have emphasized how little etomidate affected the cardiovascular system (Doenicke, Kugler et al., 1973; Doenicke, Lorenz et al., 1973; Doenicke, Wagner and Beetz, 1973; Kettler et al., 1974; Holdcroft et al., 1976). In only two studies have small decreases in arterial pressure, of 9% (Morgan, Lumley and Whitwam, 1975) and 8.5% (Rifat, Gamulin and Gemperle, 1976), been noted. These observations would suggest that etomidate is the only i.v. induction agent that induces only minor changes in the cardiovascular system. Ketamine is unusual in that it increases muscle tone which may increase venous return and, in part, be responsible for the maintenance of, or increase in, arterial pressure. Etomidate has been shown also to cause involuntary movement and increased muscle tone after injection, with a reported frequency that has ranged between 18% (O'Carroll et al., 1977) and 60% (Holdcroft et al., 1976). Rifat, Gamulin and Gemperle (1976) observed myoclonic movements in nine of 14 patients. In a study of cardiovascular variables in five patients receiving etomidate, Kettler and colleagues (1974) noted that movements made cardiovascular measurements difficult and it was necessary to hold down some of the patients, and it is difficult to understand how accurate measurements could be made under these circumstances. It is possible that etomidate has a stimulant action on the central nervous system which either maintains arterial pressure directly or maintains it indirectly as a result of the increase in muscle tone which causes an increase in the venous return to the heart.

In this present study, no movements were observed, probably because all the patients were heavily premedicated, a factor which has been shown to reduce the frequency of movements (Holdcroft et al., 1976). Arterial pressure decreased by 19% after the first injection and by 13% after the second, both changes being statistically significant. As heart rate and cardiac index remained almost unchanged, it is likely that the decrease in arterial pressure was associated with vasodilatation as indicated by the decrease in systemic vascular resistance. No measurement of myocardial contractility was attempted and it is not possible, therefore, to say if this contributed also to the decrease in arterial pressure. The decrease in systemic vascular resistance would also account for the decrease in left ventricular work. Since all these changes reduced the work of the heart, they might be regarded as desirable in patients with cardiac disease, provided the decrease in arterial pressure is insufficient to compromise the coronary circulation.

The absence of any change in heart rate was in agreement with all previous studies except that by Doenicke, Lorenz and co-workers (1973) who reported an increase in heart rate of 60% in the first 2 min. In their study, however, atropine was given just before induction and may have been responsible for tachycardia. Premedication with digoxin may have prevented any changes in heart rate in the present study.

In contrast to other induction agents, etomidate caused a transient increase in respiratory frequency, which, however, was not enough to prevent an increase in Pa_{CO_2}.

Table II compares the results of this study with previous investigations in which Althesin was given to a similar group of patients with cardiac disease (Savege et al., 1976). The similarity between the maximum percentage changes in these two groups of patients following the injection of Althesin and etomidate is striking.

Pain on injection of etomidate into a small peripheral vein has been reported in up to 81% of patients (Holdcroft et al., 1976). In this study, despite the use of a vein on the back of the hand, no patient complained of pain. This may have been a result of the slow rate of injection (over 1 min) or to premedication.

The comparison of the two groups of patients with predominantly aortic or mitral valve disease showed that the overall response to etomidate was almost identical in each group, despite the commonly held belief that they respond differently to the induction of anaesthesia.

Etomidate was found to be a reliable and effective agent for induction of anaesthesia, although in this group of patients it cannot be claimed that it offered any important advantages over the existing induction agents.

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VARIATIONS CARDIORESPIRATOIRES APRES INDUCTION DE L'ANESTHESIE PAR L'ETOMIDATE SUR DES MALADES SOUFFRANT DE CARDIOPATHIE

RESUME

On a mesuré, sur deux groups de six malades souffrant de maladie de la valvule aortique ou de la valvule mitrale, les effets cardiorespiratoires de l'étomidate. L'induction de l'anesthésie à l'aide d'étomidate à raison de 0,3 mg kg^{-1} a été suivie d'une seconde dose 10 min plus tard. Aprés la première dose, une baisse de 19% de la pression artérielle systémique a été associée à la diminution de la résistance vasculaire systémique et au fonctionnement du ventricule gauch. L'index cardiaque, la pression de l'artère pulmonaire et la pression en coin ont légèrement baissé. La pression veineuse centrale et le rythme cardiaque n'ont pas changé. La légère augmentation de la fréquence respiratoire n'a pas pu empêcher une augmentation de la Pa_{CO_2}. Après la seconde dose, les variations ont été similaires. Les deux groups de malades n'ont pas été très différents dans leurs réactions à l'étomidate. Aucun malade ne s'est plaint de douleur pendant l'injection et il ne s'est produit aucun mouvement myoclonique.

HERZ-ATMUNGSVERÄNDERUNGEN NACH NARKOSEINDUKTION MIT ETOMIDAT IN HERZKRANKEN PATIENTEN

ZUSAMMENFASSUNG

Die herz-atmungsbezuglichen Einwirkungen von Etomidat wurden in zwei Gruppen von sechs Patienten mit Aorta- oder Mitralklappenerkrankungen gemessen. Der Narkoseinduktion mit 0,3 mg kg^{-1} Etomidat folgte eine zweite Dosis 10 Minuten später. Nach der ersten Dosis wurde ein 19-prozentiger arterieller systemischer Druckabfall mit einer Abnahme des systemischen Gefasswiderstands und der linksventrikularen Herzarbeit in Zusammenhang gebracht. Herzindex, Lungenarteriendruck und Keildruck nahmen alle leicht ab. Der zentrale Venendruck und die Herzfrequenz veranderten sich nicht. Ein leichter Anstieg in der Atmungsfrequenz war unzureichend, einen Pa_{CO_2}-Anstieg zu verhindern. Nach der zweiten Dosis fanden ähnliche Veranderungen statt. Die Reaktionen der beiden Patientengruppen auf Etomidat waren nicht wesentlich unterschiedlich. Kein Patient beschwerte sich uber Schmerzen wahrend der Injektion und es traten auch keine myoklonischen Bewegungen ein.

ALTERACIONES CARDIORESPIRATORIAS DESPUES DE LA INDUCCION DE ANESTESIA MEDIANTE ETOMIDATO EN PACIENTES QUE SUFREN DE ENFERMEDAD CARDIACA

SUMARIO

Los efectos cardiorespiratorios del etomidato se midieron en dos grupos de seis pacientes que sufren de enfermedad de la válvula aórtica o mitral. La inducción de la anestesia por medio de 0,3 mg kg^{-1} de etomidato fue seguida, 10 min después, por una segunda dosis. Tras la primera dosis, se produjo una disminución del 19% en la presión sistémica arterial, junto con una reducción de la resistencia vascular sistémica y de la función del ventrículo izquierdo del corazón. En cuanto al índice cardíaco, a la presión arterial pulmonar y a la presión de la cuña, todos bajaron ligeramente. No se alteraron la presión venosa central ni el ritmo del corazón. Un ligero aumento de la frecuencia respiratoria no pudo prevenir un incremento del Pa_{CO_2}. Las alteraciones fueron similares después de la segunda dosis. No difieron de manera significativa las respuestas al etomidato de los dos grupos de pacientes. Ningún paciente se quejó de sentir dolor durante la inyección, ni tampoco ocurrieron movimientos mioclónicos.

Br. J. Anaesth. (1979), **51**, 557

OPERATIVE BLOOD LOSS AND THE FREQUENCY OF HAEMORRHAGE ASSOCIATED WITH ADENOTONSILLECTOMY IN CHILDREN: A DOUBLE-BLIND TRIAL OF ETHAMSYLATE

Y. R. Arora and M. L. M. Manford

SUMMARY

One hundred children were allocated randomly to receive either ethamsylate (Dicynene) or a placebo before undergoing adenotonsillectomy. Blood loss at operation was estimated from the haemoglobin content of swabs and aspirated fluid. Mean blood loss in the ethamsylate-treated group was not significantly less than in the controls. The frequency of secondary haemorrhage was significantly less in children treated with ethamsylate ($P < 0.01$). No side-effects were reported in either group.

Although removal of tonsils and adenoids is by far the commonest operation performed in children, little has been written about the amount of blood lost during this operation. Shalom (1964) in a review of the literature about blood loss in the 5-year period from 1958 to 1962 found more than 900 articles which referred to tonsillectomy, but of these only five mentioned measurement of blood loss during the removal of tonsils and adenoids.

Ethamsylate (Dicynene, Delandale Laboratories Limited) is a capillary haemostat which has been shown to decrease blood loss in various surgical procedures (Deacock and Birley, 1969; Arnot et al., 1975; Symes et al., 1975; MacKenney, 1979) and in patients with menorrhagia (Jaffé and Wickham, 1973; Harrison and Campbell, 1976). The use of ethamsylate in tonsillectomy was studied by de Reynier (1965) and Papatheodosslou (1973) who conducted double-blind trials in adults and children. Both found a significantly smaller operative blood loss in the patients given ethamsylate than in those receiving a placebo. Another double-blind trial of ethamsylate in adults and children undergoing tonsillectomy showed no significant difference between the operative blood losses in the two groups although fewer ligatures were used on average in the ethamsylate-treated group (Gray and Noble, 1966). More recently, Verstraete and colleagues (1977) reported no significant difference between the blood loss following ethamsylate or a placebo at tonsillectomy, adenoidectomy and adenotonsillectomy in children in a double-blind trial.

The purpose of this trial was to eliminate, as far as possible, factors known to increase bleeding and then to assess the effect of ethamsylate on operative blood loss and the frequency of primary and secondary haemorrhage in a carefully controlled series of adenotonsillectomy in children.

METHOD

Patients

One hundred children admitted to hospital for adenotonsillectomy were studied. All were admitted one day before operation. They were in good general health and none had an acute respiratory tract infection. There were 52 males and 48 females, aged between 3 and 12 yr and weighing 13.2–43.5 kg on admission. The minimum acceptable haemoglobin concentration was 11 g dl^{-1}.

The children were allocated randomly, using statistical tables, to receive either ethamsylate or a placebo before operation. Ethamsylate was supplied as 250-mg tablets and ampoules containing a solution of 250 mg in 2 ml. Identical placebo tablets of lactose and placebo ampoules containing 2 ml of physiological saline were prepared. The administration was double-blind.

Each child received either the following doses of ethamsylate or the identical placebo preparation:

two 250-mg tablets on the night before operation,
two 250-mg tablets 4 h before operation,
one 250-mg ampoule i.v. immediately after induction of anaesthesia.

Premedication and anaesthesia

Children weighing less than 30 kg received triclofos

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syrup 80 mg kg^{-1} or diazepam 0.2 mg kg^{-1} with atropine sulphate 0.03 mg kg^{-1}. Nine children who weighed more than 30 kg received papaveretum 10 mg and hyoscine 0.2 mg i.m.

Anaesthesia was conducted or supervised by the same anaesthetist for all the operations in this study. Those children who were asleep or drowsy on arrival in the anaesthetic room received an inhalation induction with oxygen and cyclopropane, while in those who were still awake anaesthesia was induced with an i.v. injection of methohexitone or thiopentone. Following the administration of suxamethonium 1.5–2.0 mg kg^{-1} i.v., the trachea was intubated with a latex armoured endotracheal tube attached to an Ozorio connector with a modified Ayres T-piece, or a Magill circuit. Anaesthesia was maintained with halothane 1.5–2.0% in nitrous oxide in oxygen.

Operative technique

All the operations were performed by the same surgeon. The adenoids were removed by curettage and a gauze swab was left in the post-nasal space until the end of the operation to act as a haemostatic. The tonsils were dissected, bleeding points secured and ligated with linen thread. Care was taken not to stain the drapes with blood, all used instruments being laid on a towel which was subsequently subjected to analysis for haemoglobin content, together with all swabs used and all fluid aspirated from the operation site. The average time for the operation was 18–20 min.

Dihydrocodeine tartrate 1–1.25 mg kg^{-1} i.m. was given after operation for pain relief.

The children left hospital on the 4th day after operation normally, but any who had evidence of bleeding remained for longer (10 children).

Laboratory estimations

Venous blood was sampled for haemoglobin concentration on the morning of operation and between 36 and 48 h after operation. The haemoglobin content of all swabs, towels and fluid collected at each operation was estimated using the E.E.L. Colorimeter (Rains, 1955; Roe, Gardiner and Dudley, 1962; Rustad, 1963; Thornton et al., 1963). All estimations were carried out by the same senior technician.

The statistical analysis of the results was carried out using Student's *t* test for the significance of the difference between means. To assess the significance of the distributions of postoperative haemorrhage and operative blood loss the Fisher exact test and the chi-square test were used respectively.

RESULTS

No significant difference was shown in mean age and weight of the two groups, or in the sex distribution (table I). The haemoglobin values before and after

TABLE I. *Clinical data and results for operative blood loss at adenotonsillectomy (mean values, n.s. = not significant)*

	Placebo (50 patients)	Ethamsylate (50 patients)	Difference between means	Statistical significance
Age (yr)	5.9 ± 0.2	6.0 ± 0.2	0.1	n.s.
Sex	M 22	M 30		n.s.
	F 28	F 20		
Weight (kg)	21.6 ± 0.7	22.3 ± 0.8	0.7	n.s.
Haemoglobin concn before op. (g dl^{-1})	12.2 ± 0.1	12.3 ± 0.1	0.1	n.s.
Haemoglobin concn after op. (g dl^{-1})	11.5 ± 0.1	11.7 ± 0.1	0.2	n.s.
Estimated blood loss				
(ml)	48.0 ± 3.4	42.6 ± 2.7	5.4	n.s.
(ml kg^{-1})	2.2 ± 0.15	2.0 ± 0.1	0.2	n.s.

TABLE II. *Haemorrhage after adenotonsillectomy (n.s. = not significant; P = level of significance)*

	Placebo (50 patients)	Ethamsylate (50 patients)	Statistical significance of distribution between groups
Primary haemorrhage	1	0	n.s.
Secondary haemorrhage	10	1	$P \leqslant 0.01$

surgery did not differ significantly between the two groups.

The mean blood loss for the placebo group was 48.0 ml (2.2 ml kg^{-1}) compared with 42.6 ml (2.0 ml kg^{-1}) in the ethamsylate-treated group. The difference between the mean values for blood loss in the two groups was not statistically significant. Figure 1 shows the distribution of the blood loss in each group; fewer ethamsylate-treated patients lost more than 3 ml kg^{-1} blood, but the difference was not statistically significant.

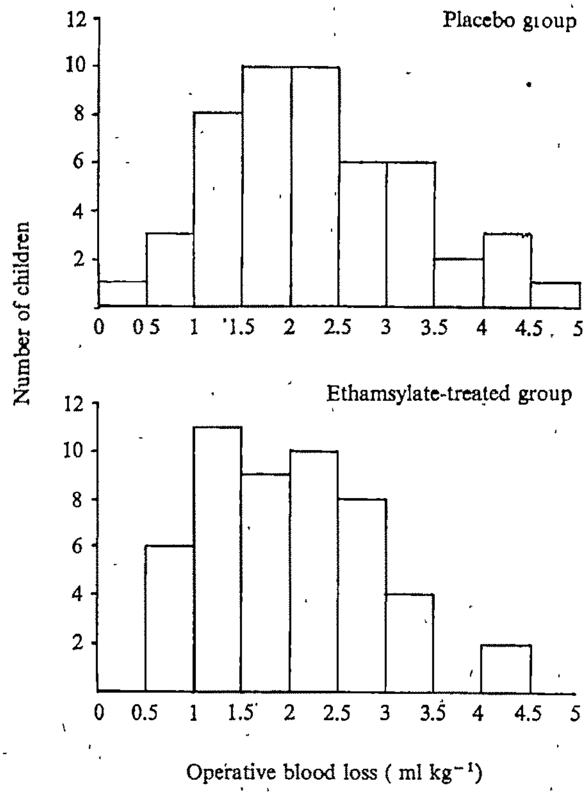

FIG. 1. Distribution of values for blood loss at adenotonsillectomy.

No correlation was demonstrated between the dose of ethamsylate (range 5.7–17.3 mg kg^{-1} (mean 11.8 mg kg^{-1}) and operative blood loss.

Only one patient in the placebo group suffered primary haemorrhage (first 24 h) and none in the ethamsylate-treated group (table II). The frequency of secondary haemorrhage (after 24 h) was significantly greater in the placebo group (10 children) compared with one in the ethamsylate group ($P \leqslant 0.01$). No patients required re-admission on account of further bleeding.

No side-effects occurred in either group.

DISCUSSION

Previous trials have indicated that the decrease in blood loss produced by ethamsylate is proportional to the blood loss with placebo (Deacock and Birley, 1969; Harrison and Campbell, 1976). Thus, ethamsylate is most effective where the untreated blood loss is great. In this series of adenotonsillectomy, operative blood losses were small in the placebo group compared with those reported by other authors carrying out dissection tonsillectomy and curettage of the adenoids under general anaesthesia in children (table III). This may account for the fact that in this trial the mean blood loss was not substantially reduced with ethamsylate.

It is not possible to compare the results of this trial directly with previous reports of the use of ethamsylate in tonsillectomy, as all differ in some respects. De Reynier (1965) studied adults, while Papatheodosslou (1973) and Gray and Noble (1966) studied adults and children, and in these trials tonsillectomy alone was performed. The work of Verstraete and co-workers (1977) is probably that most comparable to this trial, the blood loss being estimated from the haemoglobin

TABLE III. *Comparative values for blood loss during curettage of the adenoids and dissection tonsillectomy under general anaesthesia in children*

Source	No. of patients	Age range (yr)	Method of estimation	Blood loss		
				ml	Range (ml)	ml kg^{-1}
King and Story (1959)	66	4–13	Colourimetric	82.5	22–232	3.25
Ruggles (1960)	17	3–15	Radioactive ^{131}I-labelling	121	54–305	4.5
Shalom (1964)	50	2¾–9¼	Colourimetric	100	30–400	4.85
Holden and Maher (1965)	50	2–12	Volumetric and gravimetric	128	36–389	4.9
Haq and Dundee (1968)	29	4–10	Volumetric and gravimetric	100	48–213	5.0
	26	4–11	Volumetric and gravimetric	76	34–140	3.5
Arora and Manford (this study)	100	3–12	Colourimetric	48	11.5–120	2.2

content of swabs used during adenotonsillectomy in children, although Sluder tongs were used for the tonsillectomy. For this procedure they reported a mean blood loss with placebo of 4.55 ml kg^{-1} which was considerably greater than in our trial. Blood loss was not significantly less with ethamsylate, but as six different surgeons carried out the operations there is likely to have been considerable variation in blood loss within the groups.

The effectiveness of ethamsylate in reducing the blood loss at operation in adenotonsillectomy in children remains uncertain. The most striking feature of this series was the highly significant reduction in the frequency of secondary haemorrhage with ethamsylate. The use of ethamsylate to prevent haemorrhage following adenotonsillectomy appears to be worthwhile and may help to reduce the small but tragic number of deaths resulting annually from operations on the tonsils.

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PERTE DE SANG A LA SUITE D'UNE OPERATION ET FREQUENCE DE L'HEMORRAGIE ASSOCIEE A L'ADENO-AMYGDALECTOMIE CHEZ LES ENFANTS: ESSAI A DOUBLE INCONNUE DE L'ETHAMSYLATE

RESUME

Une centaine d'enfants ont été pris au hasard et il leur a été administré soit de l'éthamsylate (Dicynene), soit un placebo avant de subir une adéno-amygdalectomie. La perte de sang, lors de l'opération, a été estimée à partir de la teneur en hémoglobine des tampons et du fluide aspiré. La perte de sang moyenne dans le groupe traité à l'éthamsylate n'a pas été sensiblement inférieure à celle du groupe témoin. La fréquence d'hemorragie secondaire a été nettement moindre chez les infants traités à l'éthamsylate ($P \leqslant 0{,}01$). Il n'a été signalé aucun effet secondaire dans l'un ou l'autre groupe.

OPERATIVER BLUTVERLUST UND DIE BLUTUNGSHÄUFIGKEIT IN VERBINDUNG MIT ADENOTONSILLEKTOMIE BEI KINDERN: EIN DOPPELBLIND-VERSUCH MIT ETHAMSYLAT(DICYNEN)

ZUSAMMENFASSUNG

Hundert Kinder wurden wahllos vor einer Adenotonsillektomie entweder mit Ethamsylat (Dicynen) oder mit einem Plazebo anasthesiert. Der Blutverlust bei der Operation wurde nach dem Haemoglobingehalt der Tupfer und der Aspirationsflussigkeit geschätzt. Der mittlere Blutverlust bei der Ethamsylat-Gruppe nicht wesentlich geringer als bei der Kontrollgruppe: die Häufigkeit sekundärer Blutungen war bei den Kindern der Ethamsylat-Gruppe wesentlich geringer ($P \leqslant 0{,}01$). In keiner Gruppe traten Nebenwirkungen auf.

PERDIDA DE SANGRE EN CIRUJIA Y FRECUENCIA DE LAS HEMORRAGIAS ASOCIADAS CON LA ADENTONSILECTOMIA EN LOS NINOS: UNA PRUEBA CIEGA DOBLE CON ETAMSILATO

SUMARIO

Se seleccionó al azar a 100 niños para administrarles ya sea etamsilato (Dicineno), ya sea un placebo antes de hacerles una adenotonsilectomía. Se determinó la pérdida de sangre en la operación a partir del contenido de hemoglobina de los escobillones y de los fluídos aspirados. La pérdida media de sangre en el grupo tratado por etamsilato no era significativamente inferior a la de los controles. La frecuencia de la segunda hemorragia era mucho menor en los niños tratados por etamsilato ($P \leqslant 0{,}01$). No hubo efectos colaterales en ninguno de los dos grupos.

Br. J. Anaesth. (1979), **51**, 563P

PROCEEDINGS OF THE ANAESTHETIC RESEARCH SOCIETY

SOUTHAMPTON MEETING

MARCH 24, 1979

IN VITRO ASSESSMENT OF HEPATIC CYTOTOXICITY OF I.V. INDUCTION AGENTS

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Isolated liver cells in culture or suspension have been used to study the cytoxic effects of a number of drugs. Most previous investigators have measured enzyme leakage as the index of cellular integrity and function. Dujovne and colleagues (1970) were able to correlate the results observed in mouse liver cell culture with the known hepatotoxic potential of a number of drugs in man.

Althesin has been shown to inhibit NAD dehydrogenase and to uncouple oxidative phosphorylation in isolated mitochondria (Smith, Sweetman and Esmail, 1974). We have investigated the effects of Althesin, ketamine, minaxolone (CCI 12923), Cremophor EL and the uncoupling agent C1-CCP on isolated rat liver cells from starved male Wistar rats. The cells were prepared by collagenase digestion according to Krebs and colleagues (1974).

Aliquots of cells were incubated with alanine 10 mmol litre^{-1} in the presence of varying amounts of anaesthetic agent. After 40 min, glucose and urea production, cell ATP content and LDH leakage were measured. Althesin, ketamine and minaxolone caused a dose-dependent decrease in cell ATP content, and leakage of LDH was found to increase. Gluconeogenesis and ureogenesis decreased as a result of the decrease in ATP concentration. The changes in gluconeogenesis were found to be the most sensitive indicants of hepatic cellular response to i.v. induction agents. In the absence of any added drug, glucose production from alanine increased linearly during the 40-min incubation period. Althesin, ketamine, minaxolone and C1-CCP caused a delay in the onset of gluconeogenesis and an overall reduction in glucose production. There was no significant inhibition of glucose production by Cremophor EL.

The effects of Althesin, ketamine and minaxolone on the measured indices were similar to those produced by C1-CCP. This compound is known to exert its primary effect by uncoupling mitochondrial oxidative phosphorylation.

Using this *in vitro* model, it has been possible to correlate the relative cytotoxic effects of varying amounts of i.v. anaesthetic agents. All three drugs caused 50% inhibition of gluconeogenesis at concentrations in the range 150–300 μmol litre^{-1}.

Although enzyme leakage is a good index of cell viability, 50% inhibition of gluconeogenesis occurred at drug concentrations which caused only slight increases in LDH leakage. The concentrations of drug needed to inhibit gluconeogenesis are two orders of magnitude greater than those measured in the animal following normal i.v. sleep doses.

ACKNOWLEDGEMENT

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INHIBITION OF NEURONAL AND EXTRANEURONAL UPTAKE OF NORADRENALINE BY KETAMINE IN THE ISOLATED PERFUSED RAT HEART

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Ketamine has been tested over a wide range of concentrations for inhibition of uptake of tritiated noradrenaline into sympathetic nerve terminals (Uptake$_1$) and extraneuronal sites (Uptake$_2$) in the isolated perfused rat heart (Iversen and Salt, 1970). Both uptake processes were found to be inhibited in a concentration-dependent manner (fig. 1). Our results confirm those of previous workers with respect to Uptake$_1$ inhibition by ketamine (Miletich et al., 1973; Nedergaard, 1973). However, extraneuronal uptake into heart muscle itself was also affected significantly by ketamine and this has not been demonstrated previously. In the present study it was found that the dose–response curves for inhibition of Uptake$_1$ and Uptake$_2$ overlapped to such an extent that both processes were affected almost identically at any given concentration of ketamine. This is reflected in the IC_{50} values (concentration causing 50% inhibition) obtained from figure 1 for Uptake$_1$ inhibition (23.4 μg ml^{-1}) and for Uptake$_2$ inhibition (19.9 μg ml^{-1}). Ketamine is therefore unique amongst the sympathetic uptake blockers, which generally show a preference for one or other of the two processes. It is possible that the chronotropic and pressor side-effects of ketamine (Chang, Chan and Ganendran, 1969) may be mediated by the simultaneous inhibition of both Uptake$_1$ and Uptake$_2$.

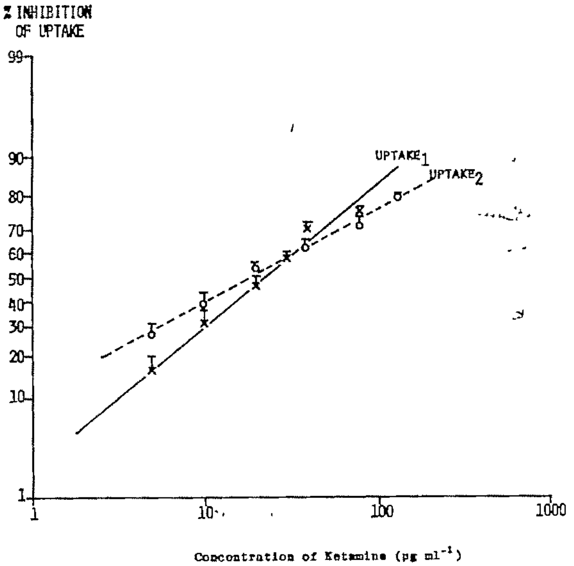

FIG. 1. Inhibition of uptake of noradrenaline by ketamine.

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MINAXOLONE: A NEW WATER-SOLUBLE STEROID ANAESTHETIC

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Minaxolone (11α-N,N-dimethylamino-2β-ethoxy-3α-hydroxy-5α-pregnan-20-one) is a new steroid anaesthetic which in laboratory animals exhibits properties similar to those of alphaxalone, the major active constituent of Althesin. Minaxolone is water soluble so that its formulation does not require Cremophor EL, the component of Althesin causing anaphylactoid reactions in dogs (Child et al., 1971), and possibly responsible for the adverse reactions to Althesin reported in man (Clarke et al., 1975).

Minaxolone produces loss of consciousness within 15 s of i.v. injection. For different species its potency increases in the order: mouse, rat, rabbit, cat and dog, monkey. With cats and dogs in blind cross-over experiments in which minaxolone was compared with other i.v. induction agents (the Althesin steroids were formulated with a propylene glycol–ethanol–water mixture instead of Cremophor EL for dogs), minaxolone was two to three times as potent as Althesin and eight times as potent as thiopentone. The profile of anaesthetic activity of minaxolone in these species was similar to that of Althesin, both steroid anaesthetics producing less respiratory depression and more rapid recovery than thiopentone. Some dogs exhibited involuntary muscle movements during anaesthesia produced by minaxolone. Similar excitatory activity occurred during anaesthesia produced by methohexitone or the Althesin steroids, but not during thiopentone anaesthesia.

Like Althesin, minaxolone has little cumulative effect when injected repeatedly. Thus in mice, in which successive doses of minaxolone were given immediately after the animals regained their righting reflex, the duration of loss of the righting reflex increased from 6 to 15.8 min between the first and 10th administration. With thiopentone the duration increased from 4 to 58 min between the first and second dose and exceeded 260 min by the fifth dose. Also, in unpremedicated cats and dogs induced with minaxolone 2.5 mg kg^{-1} i.v., a stable state of surgical anaesthesia was maintained for 6 h with minaxolone infused at a rate of 0.1 mg kg^{-1} min^{-1} and recovery was uncomplicated and moderately rapid.

Minaxolone has been given to cats and dogs in conjunction with conventional premedicants, anaesthetic adjuvants, inhalation anaesthetics and neuromuscular blocking drugs. The analgesics, particularly morphine, tended to increase the depth and duration of anaesthesia and to depress respiration at induction. In cats anaesthetized solely with minaxolone, the potency, duration of action and block characteristics of non-depolarizing neuromuscular blocking drugs were similar to those obtained in cats anaesthetized with Althesin, but the potency of suxamethonium was increased two-fold.

With i.v. injection, there was no pain on injection or vascular irritation, and no hormonal activity was demonstrated using conventional tests.

These experiments suggest that minaxolone should produce satisfactory anaesthesia in single, repeated or infused doses or when used as an induction agent in a balanced anaesthetic procedure.

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EARLY CLINICAL EVALUATION OF MINAXOLONE, A NEW STEROID I.V. ANAESTHETIC AGENT

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Minaxolone has been used for induction and maintenance of anaesthesia in 50 patients undergoing minor surgical procedures. Thirty-nine patients received atropine for premedication 27–210 min before operation (mean 75).

The first 16 patients were induced with minaxolone at a rate not greater than 5 mg/20 s, until the eyelash reflex was abolished. The duration of injection was, therefore, great (median 135 s, range 60–420) and the time to loss of consciousness and lash reflex correspondingly great (median 103, range 60–155 and median 180, range 60–455, respectively).

In subsequent patients the expected induction dose was given over 30 s and in these 34 patients consciousness was lost in 25–100 s (mean 39) from the start of injection. Mean induction dose for all patients was 0.52 mg kg^{-1} (range 0.24–0.7).

Induction was satisfactory in most instances. There was no significant change in respiratory rate measured continuously following induction in 20 patients. In 15 patients premedicated with atropine, systemic arterial pressure and heart rate were measured at 1-min intervals. The mean maximum decrease in systolic pressure was 19 mm Hg (SD 15, $t = 5.62$, $P < 0.001$) at 3–4 min, and in diastolic pressure was 9 mm Hg (SD 7.7, $t = 5.29$, $P < 0.001$) at 2–3 min. The mean maximum increase in heart rate was 20 beat min^{-1} (SD 12.6, $t = 6.04$, $P < 0.001$) at 2–3 min.

Anaesthesia was maintained with increments of minaxolone and nitrous oxide and oxygen (48 patients) or oxygen alone (two patients). The mean duration of anaesthesia and surgery was 21 min (range 7–83). In seven patients no increments were needed. In other patients one to 11 increments of 2.5–15 mg were given. Mean total dose including induction was 0.76 mg kg^{-1} (range 0.35–1.57). Fentanyl 50–100 μg was required for three patients because of movement on stimulation. Hypertonus and movement unrelated to stimuli were a problem in two.

Mean time from end of surgery to opening of the eyes was 15 min (range 2–59) and to giving birthdate correctly was 22 min (range 5–62). Mean time from last increment to opening eyes was 22 min (8–69) and to birthdate 29 min (9–72).

There were no major incidents during recovery.

We conclude that minaxolone was a safe and effective i.v. anaesthetic agent for the patients studied. The anaesthetists assessed induction and maintenance as satisfactory in 47 patients. In three there were incidents requiring intervention during induction or maintenance.

In view of the fact that recovery was prolonged in some patients having larger doses, it is likely that the total dose for surgical procedures of this type will be less than 0.8 mg kg^{-1}.

THE MECHANISM OF ACTION OF ANAESTHETIC AGENTS: A MODEL SIMULATING ENZYME CATALYSIS

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The cycloamyloses are a group of cyclic α-(1→4)-linked D-glucose polymers having six to 10 glucose residues in each "doughnut-shaped" molecule (fig. 1). They catalyse a variety of reactions and constitute a useful model for studying enzymic mechanisms (Van Etten et al., 1967). The centre of the cycloamylose molecule is hydrophobic and the mechanism of catalysis by these agents shows many of the features of normal, enzymic catalysis including stereospecificity. The catalytic rate is slow compared with most enzymic reactions, thereby allowing the various intermediates in the reactions to be studied in detail.

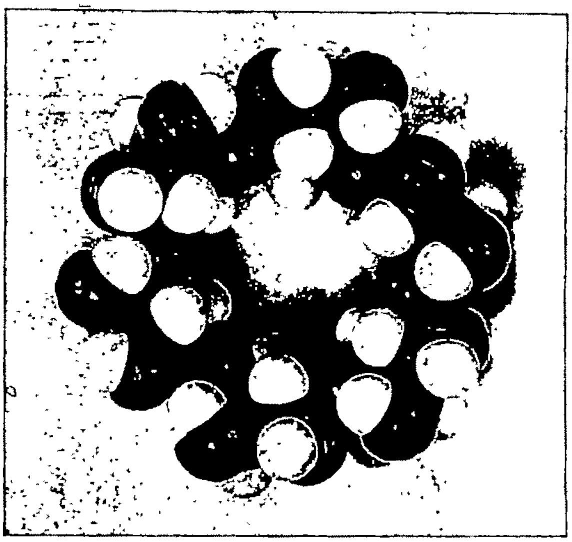

FIG. 1. A space-filling model of cyclohexamylose showing the central hydrophobic cavity.

The substrates of reactions catalysed by cycloamyloses bind with the hydrophobic core of the molecule and it was postulated, therefore, that volatile general anaesthetics may inhibit the catalytic activity of cycloamyloses.

Experiments were carried out in which the rate of hydrolysis of m-tolyl acetate was determined in the presence of either cyclohexamylose or cycloheptamylose. The catalytic rate in the presence of halothane 2.1–8.5%, chloroform 1.4–5.6%, methoxyflurane 0.2–0.8% and ether 4.8–19% was measured subsequently. With the smaller cyclohexamylose as the catalyst there was no change in the rate of reaction in the presence of any of the anaesthetics tested (except ether). However, with the larger cycloheptamylose as the catalyst the reaction rate was decreased significantly by all four anaesthetics. This inhibition was competitive in type.

Using space-filling models it was possible to show that these anaesthetics (except ether) would not readily fit into the hydrophobic catalytic centre of the cyclohexamylose but fitted readily into the larger centre of the cycloheptamylose.

These results suggest that the size of a potential hydrophobic binding site on an enzyme or receptor may be important in determining whether or not the volatile anaesthetics exert inhibitory effects. In addition it would seem that the cycloamyloses provide a useful model system for studying the molecular mechanisms involved when anaesthetics bind at hydrophobic sites.

ACKNOWLEDGEMENT

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DIFFERENCES IN CEREBRAL BLOOD FLOW AND CORTICAL ELECTRICAL ACTIVITY DURING HYPOTENSION INDUCED BY TRIMETAPHAN AND NITROPRUSSIDE IN THE CAT

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Regional cerebral cortical blood flow (rCBF) was measured in cats by the krypton clearance technique during normotension and hypotension. The e.e.g. and cerebral function monitor (CFM) were recorded (10 cats) from frontoparietal bi-polar leads on the same hemisphere as the rCBF measurements (9 cats). The electrical power in each 1-Hz interval of the frequency spectrum 1–24 Hz was calculated by computer (PDP 11-34) and the CFM trace was analysed in terms of mean level, upper level and lower level (Prior, Maynard and Brierley, 1978). Anaesthesia comprised nitrous oxide, oxygen and 0.7% inspired halothane and ventilation was controlled at normocapnic values under neuromuscular blockade with pancuronium 0.05 mg/30 min i.m.

During the normotensive stage, rCBF, e.e.g. and CFM were recorded. Hypotension was induced with practolol 0.2 mg kg^{-1} initially, followed by 0.1 mg kg^{-1} every 30 min and either trimetaphan (TMP) at a maximum rate of 10 mg kg^{-1} h^{-1} or sodium nitroprusside (NTP) to a maximum dose of 1 mg kg^{-1}, selected randomly. The duration of hypotension was limited to 90 min. If the required arterial pressures (BP) were not achieved, blood was withdrawn (mean blood removal 12.9 ± SD 7.9 ml kg^{-1}). Measurements of rCBF, e.e.g. and CFM were made at a mean BP of 40, 35, 30 and 26 mm Hg, except that BP was not reduced further in any animal which developed an isoelectric e.e.g.

rCBF was significantly greater during NTP than TMP at mean BP of 40 and 35 mm Hg. In three of the five cats subjected to TMP hypotension, the e.e.g. became isoelectric (at BP 31, 31 and 29 mm Hg), but this did not occur in any of the five animals subjected to NTP; this difference, however, was not statistically significant. The total power in the e.e.g. expressed as percentage of control was significantly less during TMP than during NTP at BP 30 mm Hg and the level of CFM trace, expressed as percentage of control, was significantly lower when TMP was compared with NTP at mean BP 35 and 30 mm Hg. Analysis of variance showed that the total power in the e.e.g. over the BP range tested was significantly lower with TMP compared with NTP ($P < 0.05$).

The present results confirm previous work in showing a larger CBF during NTP than TMP hypotension (Stoyka and Schutz, 1975; Michenfelder and Theye, 1977; Maekawa, McDowall and Okuda, 1979). In addition, it has been demonstrated that neuronal function, as assessed by electrical activity, was better maintained during NTP hypotension.

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THE EFFECTS OF DOPAMINE ON THE ERPF IN DOGS—INTERACTION WITH DROPERIDOL

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Four Beagle dogs were studied on four occasions. Anaesthesia was induced with pentobarbitone 30 mg kg^{-1} and maintained with 60% nitrous oxide in oxygen and incremental doses of fentanyl 25 μg i.v. The lungs were ventilated to normocarbia via an endotracheal tube and the bladder catheterized. E.c.g. was monitored continuously and arterial pressure measured non-invasively. Hartmann's solution 100 ml h^{-1} was infused into a vein in the hind limb. Blood samples for γ counting were removed from a fore-limb. Before measurement of effective renal plasma flow (ERPF) the dog's bladder was emptied. A γ camera was positioned over the kidney and ^{125}I-hippuran 100 μCi was given via the i.v. infusion cannula. Renograms were plotted by computer (Nuclear Data) to confirm that the kidneys were functioning normally. Nine 5-ml blood samples were collected at set intervals and concurrently with the last sample (90 min), all the urine was collected.

On all occasions two renograms and measurement of ERPF were carried out. The experimental programmes were as follows:

(1) Standard anaesthetic with 20 min infusion of dopamine 2 μg kg^{-1} min^{-1} during the second renogram and measurement of ERPF.

(2) The repeat of the above experiment with dopamine replaced by a 20-min infusion of Hartmann's solution in equivalent volumes.

(3) Droperidol 0.2 mg kg^{-1} was injected immediately after induction of anaesthesia, followed by a 20-min infusion of dopamine as in (1).

(4) Droperidol 0.2 mg kg^{-1} was injected immediately after induction of anaesthesia followed by a 20-min infusion of Hartmann's solution as in (2).

In separate experiments the effects of these procedures on cardiac output were estimated using a radioactive isotope technique.

The cardiovascular changes were similar in all four procedures. Table I shows the percentage change in ERPF from the first to the second estimate. Dopamine produced a significant increase in ERPF (paired t test) with the standard anaesthetic, but it had no significant effects on ERPF following the administration of droperidol. Droperidol did not significantly affect ERPF measured either as actual values or as percentage change.

TABLE I. *Percentage change in ERPF from the first to the second estimate*

Dog	Standard anaesthetic /saline	Standard anaesthetic /dopamine	Droperidol /saline	Droperidol /dopamine
1	+21.08	+24.06	+4.9	+0.46
2	−13.78	+21.08	−18.1	+20.59
3	−24.11	−0.22	+4.07	−18.37
4	−5.58	+21.37	−20.79	−25.53
Mean	−5.65	+16.57	−7.48	−5.71

LUMBAR EXTRADURAL INJECTION PRESSURES IN PREGNANT WOMEN

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Although the pressures in the extradural space have been the subject of wide interest and numerous investigations, one aspect which has received little attention is the pressure generated within the space at the site of injection and its relation to the spread of analgesia. Usubiaga, Wikinski and Usubiaga (1967) measured the residual pressure 2 min after extradural injection of 2% lignocaine 10 ml and reported that, in general, a higher level of analgesia was associated with larger residual pressures.

We have measured the extradural injection pressures in 34 pregnant women at or near term. In each subject before induction of labour, the extradural space was entered at L2/3 using a 17-gauge Tuohy needle. Pressure was recorded at the syringe outlet during and after injections of 1.5% lignocaine 10 ml delivered at a constant rate of 0.143–0.333 ml s^{-1} by means of a syringe pump. Injection pressures within the extradural space were derived from the recorded curves and corrections applied for the error caused by resistance to flow through the injection system.

Subjects remained in the left lateral position for 10 min after injection and then turned supine. The distribution of analgesia to pinprick was recorded 20 min after injection.

TABLE I. *Extradural injection and residual pressures in pregnant women at or near term*

	Injection pressures (cm H_2O)		
	Initial	Terminal	Maximum
Mean (±SD)	23.2 (±14.2)	28.1 (±13.5)	29.0 (±14.0)
Range	6.0–62.0	10.5–73.0	10.5–73.0
	Residual pressures (cm H_2O)		
	1 min	2 min	
Mean (±SD)	13.0 (±4.4)	11.4 (±3.7)	
Range	3.5–23.5	2.0–18.0	

From the recordings obtained the initial, terminal and maximum injection pressures and the residual pressures 1 and 2 min after injection were calculated (table I).

Although a wide range of injection pressures was observed, the pattern of pressure curves was similar. Fluctuations were synchronous with respiratory movements and maternal arterial pulse. Maximum injection pressure usually corresponded with the terminal injection pressure.

Neither injection pressures nor residual pressures were significantly related to the rate of injection over the range investigated. Analgesia was significantly more extensive on the side dependent during injection, but there was no significant correlation between the overall extent of analgesia and the rate of injection, injection pressure or residual pressure in the extradural space.

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COMPARISON OF RESPIRATORY CHARACTERISTICS DURING ENFLURANE AND HALOTHANE ANAESTHESIA

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There are several differences between clinical anaesthesia with halothane and with enflurane. This study was designed to examine differences in respiratory characteristics.

An anaesthetic circuit was devised to measure respiratory exchange. The system developed prevents fresh gas entering the reservoir bag during the inspiratory phase,

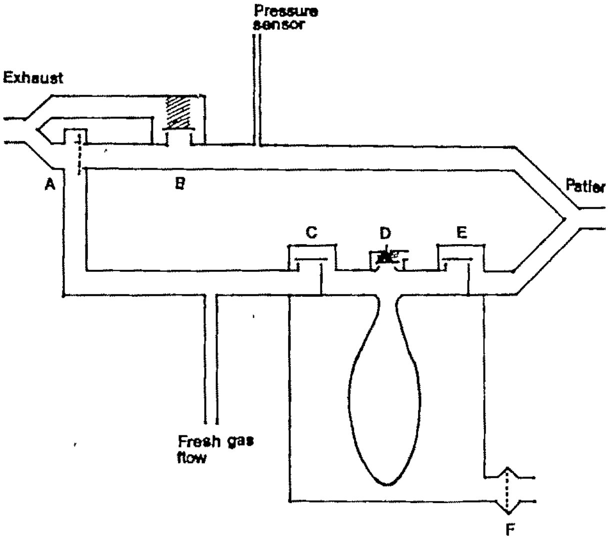

FIG. 1. Circuit diagram. A = Aga "polyvalve"; B = M.I.E. anti-pollution valve; C = weighted one-way valve; D = blow off valve set at 40 cm H_2O; E = one-way valve; F = electrospirometer head.

enabling the inspiratory tidal volume to be monitored accurately using an electrospirometer (Mercury CS6) calibrated on air. By keeping the electrospirometer head out of circuit the fresh gas flow, volatile agent and its concentration can be altered without affecting the measurements.

Two groups of patients were studied: (a) using a single volatile anaesthetic agent for surgery of the body surface, commonly tylectomy and (b) employing both agents in a crossover study during a single anaesthetic for orthopaedic procedures.

The effect of opiates, either as premedicants or when given i.v. during anaesthesia, was observed in some patients from each group.

Clinical anaesthesia was conducted by an independent anaesthetist, who controlled the depth of anaesthesia using the heart rate, arterial pressure, eye signs and absence of movement to surgical stimulus as criteria, with a minimum anaesthetic concentration sufficient to provide adequate anaesthesia for the procedure required.

A standard anaesthetic technique was employed. Anaesthesia was induced with thiopentone i.v. and maintained with 60% nitrous oxide in oxygen delivered from a monitored dial mixer through calibrated vaporizers. In addition gas flow, tidal volume, predicted respiratory rate, airway pressure, end-tidal and inspiratory carbon dioxide concentrations, heart rate, e.c.g. and arterial pressure were monitored.

Tidal volume and predicted respiratory rate were recorded continuously. End-tidal carbon dioxide concentration was recorded intermittently. The inspiratory limb of the circuit was also sampled for carbon dioxide, to ensure absence of rebreathing.

The most marked difference observed between the two agents was with respect to the rate of respiration. Enflurane produced a slower rate, characteristically 15–20 b.p.m. whilst halothane produced a rate of 30–40 b.p.m.—the latter result confirming previously published observations (Deutsch et al., 1962). Opiate premedication would appear to diminish the tachypnoea observed during halothane anaesthesia, although little effect was noted on the respiratory rate during enflurane anaesthesia. On the other hand, tidal volumes during enflurane anaesthesia were larger than with halothane (table I).

The peculiar sighing respiration characteristic of diethyl ether anaesthesia occurred intermittently in 70% of patients during anaesthesia with enflurane. A more regular sighing pattern was recorded in a quarter of all patients during enflurane anaesthesia with a frequency of one sigh every 2–5 min.

A wide range (0.4–5.0%) of concentrations of enflurane was found necessary to maintain surgical anaesthesia. Enflurane has proved to be a satisfactory alternative to halothane during clinical anaesthesia. Rapid alteration of the depth of anaesthesia is achieved easily, and respiratory changes provide a sensitive index of such variation.

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TABLE I. *Results of respiratory measurements during halothane and enflurane anaesthesia, following 20 min of surgery. Statistical analysis by F test. Enflurane group: 22 patients, 14 with endotracheal intubation; halothane group: 24 patients, 15 with endotracheal intubation*

	Enflurane		Halothane		
	Mean (±1 SD)	Range	Mean (±1 SD)	Range	*P*
Age (yr)	52 (±20)	21–90	50 (±21)	21–91	n.s.
Inspired concn (%)	1.52 (±0.9)	0.6–5.0	1.1 (±0.4)	0.6–2.0	
Respiratory freq. (b.p.m.)	20 (±3.7)	12–28	29 (±6)	15–36	<0.001
Tidal volume (ml)	240 (±80)	70–450	180 (±80)	70–460	<0.05
End-tidal CO_2 concn (%)	5.34 (±1.14)	3.8–7.7	5.24 (±1.11)	3.4–6.6	n.s.
Minute volume (ml)	4518 (±1563)	1680–8750	4399 (±1476)	2000–7820	n.s.

NEUROMUSCULAR BLOCKADE BY NEOSTIGMINE

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In a previous study we reported that neuromuscular blockade by competitive blocking agents was antagonized in the presence of 2% halothane by i.v. neostigmine 2.5 mg whereas a subsequent injection of neostigmine re-established the block (Hughes and Payne, 1977). This has been verified by further work in 24 anaesthetized patients who had given informed consent and were about to undergo urological surgery. The methods used have been described previously (Hughes, Ingram and Payne, 1976).

In nine patients, neostigmine was given during partial paralysis of the tetanic response of the adductor pollicis muscle by tubocurarine 0.1–0.24 mg kg^{-1}, dimethyl tubocurarine 0.075–0.1 mg kg^{-1} and gallamine 1.0–1.6 mg kg^{-1} when blockade had been deepened by administration of 2% halothane; groups of three patients were used for each drug. The neuromuscular block was antagonized by the first dose of neostigmine 2.5 mg, preceded by atropine 1.2 mg, but was potentiated by a second dose given 2–3 min later. Similar effects of neostigmine were obtained without halothane using groups of two patients for each of the same three drugs.

A possible explanation for the observed effects of neostigmine is that the tetanus had fully recovered after the first dose and therefore the second dose was acting on normal unblocked muscle. This hypothesis was tested in a further seven patients who were not given neuromuscular blocking drugs. Each patient received either two or three injections of neostigmine 2.5 mg when there was marked fade of the tetanic response which was accompanied by a substantial reduction in its peak height. The single twitch was either unaffected or potentiated slightly. Moreover, in four of these patients, the neostigmine block was antagonized by gallamine 10 mg with the restoration of the peak height of the tetanic response and the abolition of tetanic fade.

Furthermore, two other patients received a single dose of neostigmine 5 mg, one after gallamine 1 mg kg^{-1} when paralysis had been deepened by 2% halothane, and the other after dimethyl tubocurarine 0.075 mg kg^{-1} but without halothane. In each instance, blockade of the tetanic response was antagonized rapidly, but this was followed by a transient reduction in its peak height and a brief reappearance of tetanic fade.

These results suggest that neostigmine in doses used clinically produces an acetylcholine-induced block which could be a potential hazard in clinical anaesthesia.

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ATROPINE AND GLYCOPYRROLATE WITH NEOSTIGMINE FOR REVERSAL OF MYONEURAL BLOCK

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The quaternary ammonium anticholinergic compound, glycopyrrolate, has been shown to be an effective adjunct to antagonism by anticholinesterases of non-depolarizing neuromuscular blocking agents (Ramamurthy, Shaker and Winnie, 1972; Mirakhur, Dundee and Clarke, 1977). However, all the published studies have involved a relatively small number of patients under highly standardized conditions; a situation which obtains rarely in clinical practice. It was therefore considered important to evaluate glycopyrrolate in a "true to life" situation.

Data were obtained from 641 patients from seven centres in Northern Ireland. Neuromuscular blockade was antagonized with a mixture of neostigmine 0.05 mg kg^{-1} anh either glycopyrrolate 0.01 mg kg^{-1} or atropine 0.02 mg kg^{-1} administered on a double-blind basis.

Patients undergoing most elective surgical procedures were eligible for inclusion in the study and the 28 participating anaesthetists were free to use the technique of their choice.

Those patients receiving glycopyrrolate with neostigmine exhibited smaller changes in heart rate than those receiving atropine and neostigmine. Specifically, the initial increase and subsequent decrease in heart rate were less marked and, in addition, the proportion of patients with clinically important bradycardia was significantly larger in the atropine group. When the heart rate data of patients with pre-existing heart disease were analysed separately, the differences between glycopyrrolate and atropine became more marked.

There was no difference in the degree of antagonism of neuromuscular blockade between the two groups, but in those patients receiving glycopyrrolate there was a higher proportion with negligible oral secretions in the first 3 min after administration of neostigmine.

It was concluded that glycopyrrolate possesses advantages over atropine for use as an adjunct to reversal and that these advantages may be particularly useful in patients with pre-existing heart disease.

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ESTIMATION OF BINDING OF ^{3}H-FENTANYL TO PLASMA PROTEINS

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The extent to which a drug is bound to plasma proteins has a considerable effect on the amount of free drug available for redistribution. At present, information is lacking on the binding of fentanyl in clinical concentrations. This study describes a technique of equilibrium dialysis used to measure the amount of ^{3}H-fentanyl citrate bound to plasma protein at a plasma concentration of 1 ng ml^{-1}.

Five hundred microlitre of fresh plasma containing fentanyl citrate was dialysed against 500 μl of sodium phosphate buffer 0.1 mol $litre^{-1}$ in specially prepared Perspex cells. The plasma and buffer were separated in the cells by a sheet of Visking dialysis membrane and the cells were agitated in a water bath at 37 °C for 4 h to allow equilibration of the unbound fentanyl between plasma and buffer. Two hundred microlitre aliquots of plasma and buffer were removed and added separately to 14 ml of scintillation fluid and counted in a liquid scintillation counter for 10 min.

The percentage binding of ^{3}H-fentanyl to plasma proteins was calculated according to the equation:

$$\% \text{ binding} = \frac{C_p - C_b}{C_p} \times 100$$

where

C_p = concentration of fentanyl in plasma ("bound" + "free")

C_b = concentration of fentanyl in buffer ("free")

The effect of altering plasma pH on the amount of ^{3}H-fentanyl bound was also studied by dialysing plasma against a more acid or alkaline phosphate buffer and then measuring the change in plasma pH (table I).

TABLE I. *Percentage binding of ^{3}H-fentanyl to plasma proteins at different plasma pH values*

	Plasma pH (unit)			
	7.05	7.30	7.39	7.57
Binding (%) (±SEM)	76.9 (0.27) $n = 5$	82.5 (0.18) $n = 6$	86.6 (0.31) $n = 6$	90.6 (0.26) $n = 4$

Thus the amount of ^{3}H-fentanyl bound to plasma protein and hence the amount of free drug is influenced considerably by plasma pH. The pharmacokinetic and clinical implications of these findings will be discussed.

EFFECT OF NALOXONE ON RESPIRATORY CHANGES AFTER DIAZEPAM

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The balance of evidence suggests that naloxone does not reverse the c.n.s. depressant effect of non-opiate drugs, but there are two reports of reversal of coma and respiratory depression produced by diazepam (Moss, 1973; Bell, 1975). In a double-blind cross-over trial we have compared the effects of naloxone and saline on the respiratory changes produced by diazepam in three subjects. Sixty and 95 min following diazepam 15 mg i.v. each subject received either naloxone 15 mg i.v. or the equivalent volume of saline.

Diazepam produced significant depression of the slope of the rebreathing ventilatory response to carbon dioxide ($\dot{V}/P\mathrm{co}_2$) to 45% of control at 1 h ($P < 0.05$). This recovered to 62% of control after the first dose of naloxone and to 47% of control after saline. Following the second dose of naloxone, $\dot{V}/P\mathrm{co}_2$ recovered to 72% of control compared with 51% after saline. Average $\dot{V}/P\mathrm{co}_2$ over the 150 min after the second injection of naloxone was 88% of control compared with 58% after saline. The paired t test showed $\dot{V}/P\mathrm{co}_2$ after the first and second doses of naloxone to be significantly greater than after saline ($P < 0.05$). Also, average $\dot{V}/P\mathrm{co}_2$ over the 150 min after the second injection of naloxone was significantly greater than after saline ($P < 0.05$). The mouth occlusion pressure response to carbon dioxide, $P\mathrm{o.1}/P\mathrm{co}_2$ (Whitelaw, 1975) showed similar changes which were not statistically significant. End-tidal carbon dioxide tension during quiet breathing and inspiratory resistive loaded breathing (8 kPa litre^{-1} s) showed no significant changes after diazepam, naloxone or saline.

The results of this study suggest that a large dose of naloxone may be effective in relieving respiratory depression following diazepam by reducing depression of carbon dioxide sensitivity. This raises the possibility that respiratory depression following diazepam is mediated by the release of endogenous endorphins or that naloxone in these doses has other effects on the c.n.s. in addition to those of a specific opiate antagonist.

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DEMAND ANALGESIA FOR POSTOPERATIVE PAIN

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An apparatus has been developed to deliver small doses (0–30 μg) of fentanyl "on demand" to patients in the period immediately after operation. Every 6 min the patient is asked, by means of a pre-recorded cassette tape, to "press the button twice" if in pain. Following a positive response, a predetermined increment of fentanyl is given i.v. by a peristaltic pump, and a second message is played, telling the patient that a dose has been given. He can also call the apparatus by pressing the button once, so that a 6-min pause between doses is not mandatory. In addition to demand doses, the apparatus also delivers a programmed infusion in a dose depending upon the number of demand doses given in the previous 12 min.

An integral pneumograph is used to determine the period between successive inspirations. If this exceeds 8 s in a 1-min period, a lockout circuit prevents the apparatus inviting or delivering a drug.

Accidental overdosage resulting from component failure is prevented by two independent fail-safe systems, both of which act by interrupting the power supply to the infusion pump.

Elapsed time, total dose given (μg), respiratory monitor status and operating sequence are indicated on the front panel.

The value of the apparatus in practice has been evaluated by a simple study on 10 patients, following upper abdominal surgery. Each patient received "demand analgesia" for the first 12 h after operation. The dose of fentanyl, respiratory rate and heart rate were tape-recorded. The severity of pain was evaluated at 15-min intervals and recorded on a five-level Keele pain chart (Keele, 1948).

Nine patients achieved satisfactory analgesia, with pain scored at "slight" or less in 96% of observations, but one patient was confused for the first 4 h and scored "slight pain" or less in only 47% of observations during that period.

Cumulative dose plots show that each patient demanded fentanyl at a fairly constant rate, with considerable variation between patients. Administration rates varied between

0.26 μg min^{-1} and 1.54 μg min^{-1} (averaged over the 12-h period).

Demand analgesia provides safe, reliable relief from pain following surgery, but is not suitable for confused or irrational patients.

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CORRESPONDENCE

INADVERTENT ADMINISTRATION OF 100% OXYGEN DURING ANAESTHESIA

Sir,—I read Dr Paymaster's letter (1978) with interest as I have encountered similar difficulties with the Cape Waine, Mark III Anaesthetic Machine. Here again there is a "push–pull" switch situated on the front panel of the machine for the delivery of emergency oxygen. This button has been left pushed to the "on" position after use and this has not been noticed by another anaesthetist using the machine immediately afterwards.

The position of the switch is a hazard. Located at the front of the machine, it is liable to be pushed to the "on" position by any member of the theatre staff who leans against the machine. The switch is noiseless and the anaesthetist may be unaware that a high concentration of oxygen is being delivered to the patient. Two cases of awareness during anaesthesia have occurred as a result of this problem.

Many similar incidents must have occurred and I would support the suggestion of a warning device to guard against the machine inadvertently delivering 100% oxygen.

This problem has been notified to Cape Waine Ltd, who propose the fitting of a metal shroud to prevent accidental activation of the emergency oxygen switch.

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REFERENCE

Paymaster, N. J. (1978). Inadvertent administration of 100% oxygen during anaesthesia. *Br. J. Anaesth.*, **50**, 1268.

NALOXONE AND ACID–BASE BALANCE IN MAN

Sir,—In a recent study (Khanna and Pleuvry, 1978) naloxone was shown to produce significant changes in the acid–base state of the rabbit. Since such changes would be of considerable interest if they occured in man, a double-blind study was undertaken in healthy volunteers to compare saline with naloxone 6 μg kg^{-1} i.v.

Blood samples were taken for blood-gas analysis from the back of the hand which had been warmed in an electric blanket to ensure rapid circulation. Arterialized venous blood pH and $P\mathrm{CO}_2$ were measured using a Radiometer micro-analyser; haemoglobin concentration was measured using standard hospital techniques and pulse and arterial pressure were measured at frequent intervals throughout the study.

After consistent baseline values had been obtained the volunteers were given saline or naloxone i.v. Further blood samples were taken at 10-min intervals for the subsequent 30 min and also at 60 min after injection. Drug or saline injections were always given in the arm opposite to that used for blood sampling. At least 1 week elapsed between each of the two treatments and six volunteers (three of each sex) took part in the trial.

Naloxone had no significant effects upon the measurements obtained (table I) and thus the acid–base problems seen in the rabbit would not appear to be relevant to man.

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Khanna, V. K., and Pleuvry, B. J. (1978). A study of naloxone and doxapram as agents for the reversal of neuroleptanalgesic respiratory depression in the conscious rabbit. *Br. J. Anaesth.*, **50**, 905.

RECTAL KETAMINE IN PAEDIATRIC ANAESTHESIA

Sir,—The induction of anaesthesia in the frightened or difficult child can be difficult and unpleasant for all involved. In most European countries rectal thermometers are used frequently for children who, therefore, accept rectal application of drugs without undue distress. We have used ketamine rectally for induction of anaesthesia in 150 children undergoing surgery for inguinal hernia (61), ectopic testis (37), hydrocoele (25) and various other operations.

Atropine and diazepam 0.2 mg kg^{-1} were given i.m. 1 h before the rectal administration of ketamine 8–10 mg kg^{-1} (to a maximum of 150 mg). A 1% solution

TABLE I. *Effect of saline and 6 μg kg^{-1} naloxone on the arterialized venous blood pH and $P\mathrm{CO}_2$ in man. *Readings are expressed as the change from the values before injection for each individual. Results are means ± standard errors of six experiments*

		Saline	Naloxone
Before injection	pH (unit)	7.459 ± 0.016	7.462 ± 0.009
	$P\mathrm{CO}_2$ (kPa)	4.82 ± 0.30	5.16 ± 0.07
After injection*			
10 min	pH (unit)	+0.027 ± 0.023	−0.018 ± 0.011
	$P\mathrm{CO}_2$ (kPa)	−0.05 ± 0.19	−0.03 ± 0.16
20 min	pH (unit)	−0.006 ± 0.017	−0.006 ± 0.013
	$P\mathrm{CO}_2$ (kPa)	+0.02 ± 0.20	+0.12 ± 0.08
30 min	pH (unit)	−0.039 ± 0.015	+0.007 ± 0.021
	$P\mathrm{CO}_2$ (kPa)	−0.09 ± 0.12	+0.19 ± 0.21
60 min	pH (unit)	−0.035 ± 0.015	−0.001 ± 0.014
	$P\mathrm{CO}_2$ (kPa)	+0.36 ± 0.27	+0.08 ± 0.08

was used for children weighing less than 15 kg and a 5% solution for those weighing more. When the required level of sedation was obtained, anaesthesia was maintained and controlled by the use of enflurane in nitrous oxide and oxygen, with spontaneous ventilation via a face mask. In 48 patients the trachea was intubated following the administration of suxamethonium. In 22 children artificial ventilation was employed with the aid of competitive neuromuscular blocking drugs.

The interval from rectal administration of ketamine to loss of verbal contact was 378±9 s ($n = 67$)—an interval similar to that following i.m. administration.

The children did not tolerate the face mask without moving until at least 8 min (average 9 min 28 s±18 s ($n = 59$)). Heart rate increased from 97±11 to 110±14 beat min^{-1} and arterial pressure from 94±0.8 to 101±1 mm Hg. The duration of these effects could not be determined, since inhalation anaesthesia was started immediately.

The concentrations of enflurane required were 40% less than those required in the absence of ketamine. Surgical conditions were not changed by the use of ketamine.

The children responded to simple commands 18 min 36 s±16 s after terminating the administration of enflurane.

Excessive salivation was frequent. It was concluded that a larger dose of atropine should be given before administering ketamine rectally. Hypotonia, without respiratory depression, occured in four very young children. Vomiting occurred after operation in 16. No rectal irritation was observed.

Induction was judged excellent in 139, good in seven and fair in four instances. Amnesia for induction was complete in 75% of the pateints.

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LITHIUM, ANAESTHESIA AND ECT

Sir,—Jephcott and Kerry (1974) have described a patient who had taken lithium carbonate and who could not be roused for more than 2 h after modified ECT and who was drowsy for the remainder of the day. The plasma lithium concentration during the episode was 3.4 mmol litre^{-1} and it seems likely that the unusually prolonged effect of the anaesthetic was associated with this. Subsequently, Mannisto and Saarnivaara (1976) found that, in mice, lithium prolonged methohexitone-induced sleep. Jephcott and Kerry (1974) were unable to explain the high plasma lithium concentration in their patient, since she had previously been well controlld.e Since anaesthetics affect membrane permeability, it may be postulated that such drugs cause short-term changes in the distribution of lithium.

Six patients suffering from manic depression who were undergoing modified ECT and who were taking lithium carbonate were investigated. ECT treatment was given at 11.00 h, lithium carbonate having been withheld from 14.00 h the previous evening. Venous blood samples were taken immediately before and 1 h and 3 h after ECT. Ammonium heparin was used as anticoagulant. Premedication was with atropine 0.6 mg given 30 min before ECT. Methohexitone sodium 100 mg followed by suxamethonium bromide 30 mg i.v. were used for anaesthesia. Plasma lithium concentrations were determined by atomic emission spectrometry.

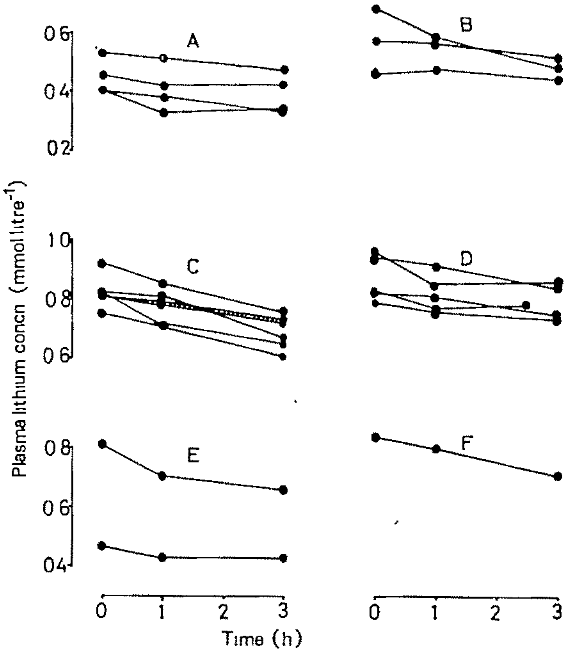

FIG. 1. Decay curves of plasma lithium concentration in six patients treated by ECT at time 0.

In no patient (fig. 1) was treatment associated with a significant deviation from the expected exponential concentration decay curves. We conclude that there is no evidence that modified ECT affects blood lithium concentrations.

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BOOK REVIEWS

Cerebral Vascular Smooth Muscle and its Control (Ciba Foundation Symposium No. 56–new series). Published (1978) by Elsevier, Excerpta Medica, North Holland. Pp. 400; illustrated; indexed. Price US$ 35.50.

This book contains a widely ranging review of much current research and thinking on cerebral blood flow, metabolism and regulating factors. Like many proceedings in similar symposia, there is a wide range of quality, digestibility and clinical relevance in the articles published. Much of the information is obtainable in fuller papers published by the same authors.

The opening half of the book describes factors affecting cerebral vascular smooth muscle and blood flow; the second half is devoted to metabolism.

Evidence presented suggests that oxygen may be most important in regulating arteriole diameter, but that capillaries are more likely to be controlled by the interaction of several factors, including K^+ and H^+ activity.

The book provides a successful introduction to the new techniques in quantifying aspects of cerebral metabolism and leaves little doubt that this is an area where great advances will be made in the next few years. The (^{14}C) deoxyglucose technique has been used to show that the functional activity of the central nervous system regulates the local rate of energy metabolism and thence local blood flow is adjusted to meet the local metabolic demand. Nevertheless, many inhalation anaesthetics produce a blood flow in excess of metabolic requirements.

The book contains useful information and deserves a place in selected reference libraries.

R. Greenbaum

Adverse Response to Intravenous Drugs. By J. Watkins and A. Milford Ward. Published by Academic Press. Price £8.20.

This volume is the result of a Symposium held in the University of Sheffield Medical School, June 1977, at which invited participants discussed the frequency and mechanisms of adverse reactions to i.v. anaesthetic agents and plasma expanders. The book is divided into four sections dealing with clinical aspects and pharmacokinetics, incidence, mechanisms and management. The present volume should not be confused with a further symposium, "Adverse responses to intravenous agents", Sheffield, July 1978 (Watkins and Clarke, 1978).

As the authors state in their foreword, the reactions and mechanisms discussed fall into the category of "qualitative abnormality in response". These reactions form a heterogeneous group, being neither predictable in relation to the normal pharmacology of the drug, related to dose, nor detectable in the normal toxicological screening during development and manufacture. Put more simply, immune responses are involved—probably.

For those looking for an account of the problems involved in unexpected reactions to i.v. agents the book is helpful. However, the reader should not hope to discover definitively how immunology relates to anaesthesia. A glossary of terms would be helpful; anaphylaxis, anaphylactoid, allergoid, allergy, histaminoid, sensitivity and hypersensitivity are used by some contributors as interchangeable terms, whereas other authors seem to imply specific meanings. Perhaps among those in the know these semantic problems are unimportant. However, for the tyro such jargon seems to raise resistance. It would be a pity, therefore, if *Adverse Response to Intravenous Drugs* is dismissed for such reasons.

The sections on plasma substitutes and histamine release, the latter by Lorenz and Doenicke from Germany, are valuable contributions. For various reasons plasma substitutes have never been as widely used in Britian as in Europe. Although the risk of a fatal reaction seems very small, the frequency of other unwanted responses to plasma substitutes is such that perhaps we should be grateful that Ringer–lactate infusion is still in vogue in Britian.

Publication of a symposium is often criticized as being too little and too late and always anticipating next year's meeting. However, the present volume is the first of its kind and has appeared rapidly, although already overtaken by the next symposium, and its content is full. On balance, therefore, the book may be recommended for those interested in such problems.

Leo Strunin

REFERENCE

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Pain Relief in Labour (3rd edn). By D. D. Moir. Published (1978) by Churchill Livingstone. Pp. 122; illustrated; indexed. Price £1.95.

This book is written primarily for midwives in the United Kingdom. It is accurate and up-to-date, as were previous editions. The opening chapter deals briefly with "History" and in an interesting manner. "Psychoprophylaxis and Allied Methods" are discussed succinctly. In "Analgesics, Sedatives, Tranquillizers—General Principles", and "Individual Sedatives", the author unequivocally sets out the important points and comments on the choice of drugs. "Inhalation Analgesia" is a thoroughly practical review of this important, and uniquely British, contribution to pain relief in labour. "Local Anaesthetics and Regional Anaesthesia" considers comprehensively the midwife's responsibilities, especially in relation to extradural block. "General Anaesthesia and Resuscitation" is the most important chapter of all, explaining in detail the midwife's vital role in helping the anaesthetist—help which can contribute so much to a reduction in mortality and morbidity.

This short book is written clearly with a few well-produced diagrams and tables. Dr Moir has mainly eschewed personal prejudice, although not hesitating to comment forcefully where necessary. This is a suitable text for any pupil midwife, whatever her anaesthetist teacher's preconceptions. Indeed, the sound advice in this book will be valuable to any anaesthetist concerned with this subject.

Michael Rosen

Anesthetic Accidents: Case Studies. By T. Gordh and J. W. Mostert. Published by Little Brown and Company, 34 Beacon Street, Boston, Massachusetts 02106, U.S.A. Subscription $ U.S. 35 per year.

This record of anaesthetic accidents has to be compulsory reading, not only for anaesthetists, but also for all involved with operating rooms. The text is not particularly well written, but the stark reality of each case history has lessons for every clinician. It is of course true that most anaesthetists have avoided the ultimate disaster; whether by good luck or by good judgement may perhaps be a matter for debate, but what is clear from examination of these case histories is that most deaths were avoidable and that inexperience, lack of technical expertise, absence of fundamental knowledge and elemenatry errors of judgment as well as occasionally the basic arrogance of the clinician unwilling to accept the opinion of a nurse were significant factors in the conversion of minor mishaps into major catastrophes.

The devastating feature of these records is that a substantial number of the victims were admitted to hospital for elective minor surgery and there can be no doubt that under these circumstances when a patient suffers a major injury then someone is at fault; either the patient should not have been listed for elective surgery or an error was made in the handling of the case. Perhaps the saddest aspect is the fact that many of the victims were either children or young adults in good health.

What this book makes abundantly clear, even if it is not explicitly stated, is that the place of the skilled anaesthetist is in the operating room and those seekers after status who prefer to spend their time in the intensive care unit or elsewhere in the hospital, rather than in the operating theatres, might consider whether it is right that healthy young patients should be allowed to die or, worse, converted into vegetables, while they devote their attention to patients whose hold on life may be tenuous and whose need for medical supervision is less vital. Perhaps if anaesthetists spent a little more time in the operating rooms there would be less need for intensive care units.

Most, but not all, case histories are accompanied by a comment and it is sometimes difficult to decide the basis on which the comment is provided, especially as some seem scarcely relevant. In addition, scattered throughout the text are a number of undocumented *ex cathedra* statements which, to say the least, are lacking in proof. For example, it is claimed on p. 99 that there is still a British school of thought that argues that cigarette smoking has not yet been proved carcinogenic even though the overwhelming evidence of its carcinogenicity is accepted by most people. It seems unlikely that this attitude is specifically British; furthermore, it is common experience that compared with their North American and European colleagues, British doctors are remarkably abstemious in their smoking habits.

Elsewhere, careless proof reading has led to some virtually unintelligible sentences remaining in the text and one or two references are not relevant to the material presented. Nevertheless, compared with the overall presentation these are minor defects which can easily be corrected in a future edition. Every anaesthetist needs a copy of this monograph.

J. P. Payne

Sir Robert Macintosh's Lumbar Puncture and Spinal Analgesia—Intradural and Extradural (4th edn). By J. Alfred Lee and R. S. Atkinson. Published (1978) by Churchill Livingstone, Edinburgh, London, New York. Price £10.

The first edition of Professor Macintosh's monograph appeared in 1951. The 4th edition, published under the joint authorship of Dr J. Alfred Lee and Dr R. S, Atkinson, preserves the greater part of Professor Macintosh's fluent and dynamic text and most of Miss McLarty's superb anatomical drawings. It know includes additional chapters dealing with the technique and practice of extradural block. These will be welcomed not only because of the growing importance of the technique in surgical, obstetric and therapeutic practice, but also because of the authors' widely acclaimed experience of teaching in this field.

In their preface Drs Lee and Atkinson lament that the withdrawal of Professor Macintosh from the labour of revision has deprived this edition of his wise counsel, vast experience and of his powers of literary expression. This is readily perceptible in the added chapters on extradural block which make for harder reading, probably on account of the inclusion of so many references which detract from the personal authority of the authors and seriously affect the fluidity of the text. The book is aimed at the "working anaesthetist, be he a trainee or one well-established in his specialty". He is nevertheless likely to be a tyro in the technique of extradural block and he would certainly expect more detailed and specific instructions than are given in these added chapters. Some original illustrations to match the interest, quality and relevance of those in the earlier part of the book would have been helpful: unhappily only three appear in the extradural chapters and these are borrowed from other publications. The impression is given that the authors, with characteristic modesty, appear loath to draw on their own extensive teaching experience in favour of including many references to the work of other experts in this field. This does not accord with Professor Macintosh's clear and didactic style in the earlier chapters.

The authors attempt to establish the term "intradural" as a synonym for "subarachnoid", justifying this on the grounds of etymological rectitude. It remains to be seen whether the innovation receives wide approval, particularly as it fails to allow for the existence of the potential subdural space (mentioned on p. 40), injections into which have been used for therapeutic purposes. Inadvertent injection into this space has been advanced as the explanation of the rare but worrying complication of "massive extradural block". The labelling of some diagrams has not been altered to accord with the new terminology and further inconsistencies occur in the text. Whatever the reasons for the change, this reviewer suggests that most readers would have preferred that the universally accepted old terminology be continued, in the interests of clarity.

Nevertheless, despite some spelling errors missed by the proof-readers, one must warmly recommend the 4th edition of this book as continuing to provide an unrivalled account of the anatomical details essential to those learning either form of spinal analgesia, with the welcome addition of a synopsis of information on all the current applications of extradural techniques.

Andrew Doughty

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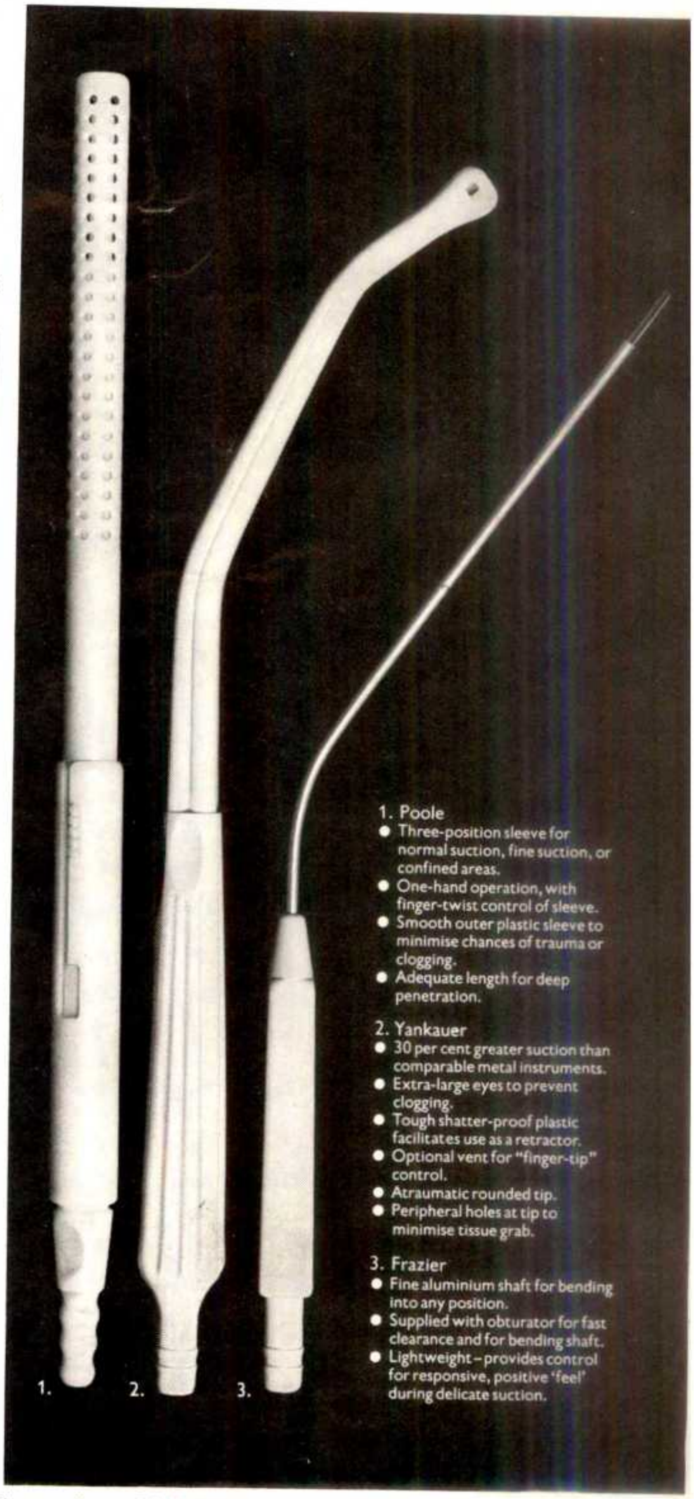

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